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Office of Regulatory Policy
HFD-7
5600 Fishers Lane (Rockwall II Rm 1101)
Rockville, MD 20857

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 7,109,205 was filed on August 7, 2007, under 35 U.S.C. § 156. It is noted that applicant also filed applications for patent term extension for NDA 22-081 in U.S. Patent Nos. 5,703,017, 5,840,722, and 5,932,730, pursuant to 37 CFR 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, LETAIRIS™(ambrisentan), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to Raul Tamayo at (571) 272-7728 (telephone) or (571) 273-7728 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Martin L. Katz
Wood, Phillips, Katz, Clark & Mortimer
Citigroup Center, Suite 3800
500 West Madison Street
Chicago, IL 60661-2511

DATE 1-9-08 APPLICATION NUMBER 10/602275

DOC CODE TERM.REQ DOC DATE 8-7-07

DELIVER THE ATTACHED FIFLE/DOCUMENT TO THE TC SCANNING CENTER

CONTRACTOR: THE ATTACHED FILE/DOCUMENT MUST BE INDEXED AND SCANNED INTO IFW WITHIN **8** WORK HOURS; UPLOADING OF THE SCANNED IMAGES SHOULD OCCUR NO LATER THAN **16** WORK HOURS FOLLOWING RECEIPT OF THIS REQUEST

AFTER SCANNING, ORIGINAL DOCUMENTS SHOULD BE BOXED IN ACCORDANCE WITH INSTRUCTIONS

HDP/SB/17 (01-07)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2007

Effective 2/8/2006. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120

Complete if Known	
Application Number	Patent No. 7,109,205
Filing Date	June 24, 2003 (Issue Date: September 19, 2006)
First Named Inventor	Hartmut Riecke
Examiner Name	
Art Unit	
Attorney Docket No.	

RECEIVED AUG 07 2007 PATENT EXTENSION ACCEPTED

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 01-0025

Deposit Account Name: Abbott Laboratories

The Director is authorized to: *(check all that apply)*
☒ Charge fee(s) indicated below ☒ Credit any overpayments
☒ Charge any additional fee(s) during the pendency of this application
☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1011	300	2011	150	Utility filing fee	
1012	200	2012	100	Design filing fee	
1013	200	2013	100	Plant filing fee	
1014	300	2014	150	Reissue filing fee	
1005	200	2005	100	Provisional filling fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	=	Fee Paid
Total Claims		-20 **	0	X		=	0
Independent Claims		-3 **	0	X		=	0
Multiple Dependent						=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	** Reissue independent claims over original patent
1205	50	2205	25	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1020	2253	510	Extension for reply within third month	
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	
1403	1000	2403	500	Request for oral hearing	
1452	500	2452	250	Petition to revive – unavoidable	
1453	1500	2453	750	Petition to revive – unintentional	
1462	400	1462	400	Petition fee under 37 CFR 1.17(f)	
1463	200	1463	200	Petition fee under 37 CFR 1.17(g)	
1464	130	1464	130	Petition fee under 37 CFR 1.17(h)	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
Other fee (specify) Application of Extension of Patent Term					1,120

**Reduced by Basic Filing Fee Paid* SUBTOTAL (3) ($)1,120

4. SEARCH/EXAMINATION FEES

1111	500	2111	250	Utility Search Fee
1112	100	2112	50	Design Search Fee
1113	300	2113	150	Plant Search Fee
1114	500	2114	250	Reissue Search Fee
1311	200	2311	100	Utility Examination Fee
1312	130	2312	65	Design Examination Fee
1313	160	2313	80	Plant Examination Fee
1314	600	2314	300	Reissue Examination Fee

SUBTOTAL (4) ($)0

SUBMITTED BY Complete *(if applicable)*

Name (Print/Type)	John D. Conway	*Registration No. (Attorney/Agent)*	39,150	*Telephone*	508-688-8046
Signature	John D. Conway			*Date*	August 7, 2007

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 7,109,205
Title:	CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE
Issue Date:	19 September 2006
Inventors:	Hartmut Riechers, Dagmar Klinge, Wilhem Amberg, Andreas Kling, Stefan Müller, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Wolfgang Wernet, Liliane Unger, and Manfred Raschack
Patent Owner:	Abbott GmbH & Co. KG
Unit:	OPLA
Attn:	Mary C. Till

7 August 2007

Mail Stop **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

In support of the Application for Patent Term Extension of U.S. Patent No. 7,109,205, Applicant submits the following:

1. PTE Application (being submitted as one original and two additional copies thereof)
2. Exhibits A-L
3. Duplicate Fee Transmittal Sheet

Applicant certifies that the two additional copies are identical to the original being submitted.

Respectfully submitted,

John D. Conway
Registration No. 39,150
Attorney for Applicant
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Tel.: 508-688-8046
Fax: 508-688-8110

Enclosure

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 7,109,205
Title:	CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE
Issue Date:	19 September 2006
Inventors:	Hartmut Riechers, Dagmar Klinge, Wilhem Amberg, Andreas Kling, Stefan Müller, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Wolfgang Wernet, Liliane Unger, and Manfred Raschack
Patent Owner:	Abbott GmbH & Co. KG
Unit:	OPLA
Attn:	Mary C. Till

Mail Stop **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Abbott GmbH & Co. KG ("Applicant"), of Max-Planck-Ring 3, 65205 Wiesbaden, Germany, submits this application for extension of patent term of U.S. Patent No. 7,109,205 ("U.S.'205") under 35 U.S.C. §156. The relevant facts establishing the authority of Applicant to file this application for extension of patent term in accordance with 37 C.F.R. §1.730 are set forth below:

- Between 24 June 2003 and 12 October 2003, Hartmut Riechers, Dagmar Klinge, Wilhem Amberg, Andreas Kling, Stefan Müller, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Wolfgang Wernet, Liliane Unger, and Manfred Raschack (the inventors of the subject matter claimed in U.S. Patent No. 7,109,205) assigned to Abbott GmbH & Co. KG all right, title and interest in their invention. This assignment was recorded in the

United States Patent and Trademark Office on 11 December 2003 at Reel 014778, Frame 0028. A copy of this assignment is attached as Exhibit A.

- The Investigational New Drug application ("INDA") for ambrisentan was originally filed by Myogen, Inc. Effective on 17 November 2006, Myogen, Inc. was acquired by Gilead Sciences, Inc. ("Gilead") and became a wholly owned subsidiary known as Gilead Colorado, Inc. A copy of the New Drug application ("NDA") submission letter indicating this fact is attached as Exhibit B.

- Gilead is the exclusive licensee to U.S. '205.

- Gilead is the sponsor of the drug product, LETAIRIS™ (ambrisentan), for which the FDA granted regulatory approval and which forms the basis of this patent term extension. A copy of the approval letter is attached as Exhibit C.

- Applicant is authorized by Gilead to rely on its activities and the activities of its predecessor, Myogen, Inc., before the Food and Drug Administration ("FDA") for regulatory review activities. Gilead has executed a statement authorizing reliance by Applicant on such activities of Gilead. A copy of this statement is attached as Exhibit D.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §§1.740 to 1.741. The formal requirements of 37 C.F.R. §1.740 are specifically set out below.

1. Identification of Approved Product [37 C.F.R. §1.740(a)(1)]

The approved product is LETAIRIS™ (ambrisentan) 5 and 10 mg tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. See the approved label for LETAIRIS™ tablets provided as Exhibit E. Ambrisentan is the active ingredient in LETAIRIS™ tablets. Ambrisentan is further identified as follows:

A. Chemical Name

The chemical name for ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

The CAS registry number for ambrisentan is 177036-94-1.

B. Generic Name

The generic name of the active ingredient in LETAIRIS™ tablets is ambrisentan. Ambrisentan is the U.S. Adopted Name (USAN) and International Nonproprietary Name (INN) for this compound.

C. Molecular Formula

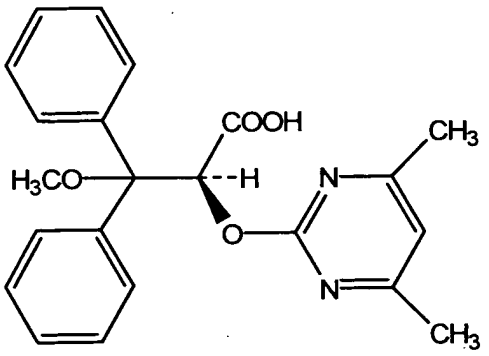
The molecular formula of ambrisentan is $C_{22}H_{22}N_2O_4$.

D. Molecular Weight

The molecular weight of ambrisentan is 378.42.

E. Structural Formula

The structural formula of ambrisentan is:



F. Product Ingredients

Ambrisentan is the active ingredient in LETAIRIS™ tablets, as provided in the approved label text attached as Exhibit E. As provided in Exhibit E, LETAIRIS™ tablets further contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. As further provided in Exhibit E, LETAIRIS™ tablets have a film coating containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

2. Federal Statute under which Regulatory Review Occurred [37 C.F.R. §1.740(a)(2)]

The approved product, LETAIRIS™ tablets, was subject to regulatory review under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §355(b)(1), as amended.

3. Date of Permission for Commercial Marketing [37 C.F.R. §1.740(a)(3)]

LETAIRIS™ product was approved by the FDA for commercial marketing pursuant to Section 505(b)(1) of the FFDCA on 15 June 2007. A copy of the letter from the FDA to Gilead, dated 15 June 2007, setting forth the approval of the product is attached as Exhibit C.

4. Identification of Active Ingredient and Certifications [37 C.F.R. §1.740(a)(4)]

(a) The active ingredient of LETAIRIS™ is ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid, having the structure depicted in Section 1 above.

(b) Ambrisentan has not been approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act, prior to the approval granted on 15 June 2007.

(c) The use for which the product is approved is as follows: "LETAIRIS™ is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening." See the approved label for LETAIRIS™ tablets provided as Exhibit E.

5. Statement of Timely Filing [37 C.F.R. §1.740(a)(5)]

The present application for extension of patent term is being submitted within the sixty-day period permitted for submission under 37 C.F.R. §1.720(f). The FDA approved commercial marketing and use of the approved product, LETAIRIS™ tablets, on 15 June 2007. The sixty-day submission period ends on 13 August 2007. As demonstrated by the signed Certificate of Hand-Delivery, this application for extension of patent term is timely submitted.

6. Identification of Patent for which Extension is Sought [37 C.F.R. §1.740(a)(6)]

U.S. Patent No:	7,109,205
Title:	CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE
Issue Date:	19 September 2006
Expiration Date:	7 October 2015
Application No.:	10/602,275
Application Filing Date:	24 June 2003 (effective filing date 7 October 1995)
Inventors:	Hartmut Riechers, Dagmar Klinge, Wilhem Amberg, Andreas Kling, Stefan Müller, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Wolfgang Wernet, Liliane Unger, and Manfred Raschack
Patent Owner:	Abbott GmbH & Co. KG

7. Patent Copy [37 C.F.R. §1.740(a)(7)]

A copy of U.S.'205, the patent for which extension is being requested, is attached as Exhibit F. This copy contains the entire specification (including claims) for U.S.'205. There are no drawings in U.S.'205.

8. Disclaimer and Post-Issuance Activity Statement [37 C.F.R. §1.740(a)(8)]

(a) Terminal Disclaimers were filed on 24 August 2005 disclaiming any term of the U.S.'205 which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 5,932,730; U.S. Patent No. 6,197,958; or U.S. Patent No. 6,600,043. A copy of each Terminal Disclaimer is attached as Exhibits G-1 to G-3.

(b) A patent term adjustment, under 35 U.S.C. 154(b), of 261 days was recorded. Under 35 U.S.C. 154(b)(2)(B), no patent term of which has been disclaimed

beyond a specified date may be adjusted under this section beyond the expiration date specified in this disclaimer.

(c) A Certificate of Correction was requested, but the Certificate has not been issued as of yet for U.S.'205.

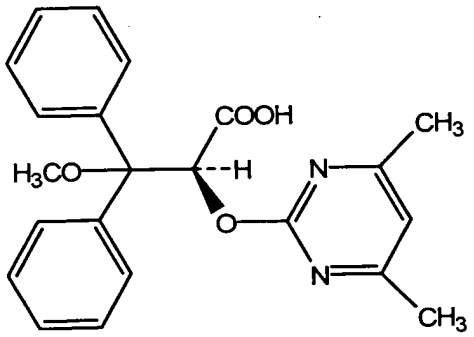
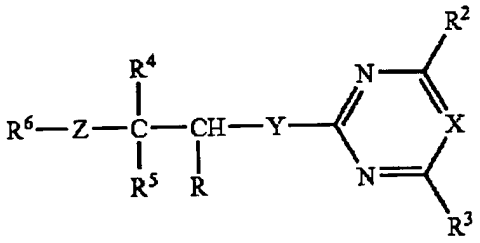
(d) U.S.'205 has not been subject to a Reexamination Proceeding.

(e) Maintenance fees for U.S.'205 patent are not yet due and have not yet been paid.

9. Statement Showing How the Claims of the Patent Cover the Approved Product [37 C.F.R. §1.740(a)(9)]

The statements in this section are provided solely to comply with the requirements of 37 C.F.R. § 1.740(a)(9). These comments are not an assertion or an admission by the applicant as to the scope of the listed claims, or as to whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale or the importation of any product.

U.S.'205 has compound-per-se claims and pharmaceutical composition claims related to the approved product. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product. The elements of the claims which embrace LETAIRIS™ product are shown in bold for convenience.

Claim 1	Ambrisentan
A compound having the formula:	
wherein:	
	
X is CH;	X is CH
Y is oxygen;	Y is oxygen
Z is oxygen;	Z is oxygen
R is CO_2H;	R is carboxyl (COOH, which is the same as CO_2H)
R^2 is methyl;	R^2 is methyl
R^3 is methyl;	R^3 is methyl
R^4 is phenyl;	R^4 is phenyl
R^5 is phenyl;	R^5 is phenyl
R^6 is methyl;	R^6 is methyl
or a pharmaceutically acceptable salt thereof.	

Claim 1 embraces the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets.

Claim 2

The compound of claim 1, wherein said compound is an optically active enantiomer.

Claim 2 embraces the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated in the approved label provided as Exhibit E, ambrisentan contains a single chiral center determined to be in the (S) configuration.

Claim 3

The compound of claim 2, wherein the enantiomer is the S enantiomer.

Claim 3 embraces the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated in the approved label provided as Exhibit E, ambrisentan contains a single chiral center determined to be in the (S) configuration.

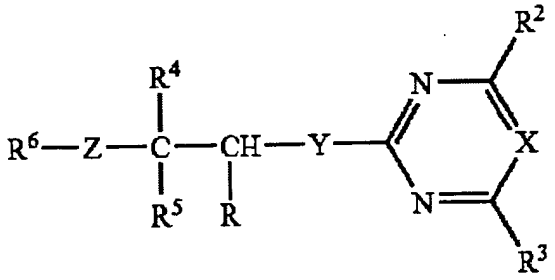
Claim 4

The compound of claim 3, wherein the enantiomer is the pure form of the S enantiomer.

Claim 4 embraces the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated in the approved label provided as Exhibit E, ambrisentan contains a single chiral center determined to be in the (S) configuration.

Claim 7

A pharmaceutical composition comprising a compound having the formula:



wherein:

X is CH;

Y is oxygen;

Z is oxygen;

R is CO_2H;

R^2 is methyl;

R^3 is methyl;

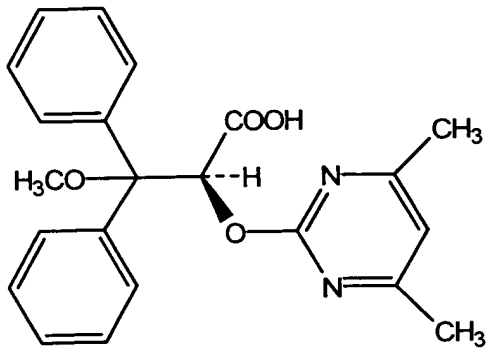
R^4 is phenyl;

R^5 is phenyl;

R^6 is methyl;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Ambrisentan



X is CH

Y is oxygen

Z is oxygen

R is carboxyl (COOH, which is the same as CO_2H)

R^2 is methyl

R^3 is methyl

R^4 is phenyl

R^5 is phenyl

R^6 is methyl

Claim 7 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. See attached Exhibit E. (A Certificate of Correction is pending related to the superscript denominations of R^2-R^6.)

Claim 8

The composition of claim 7, wherein said composition is suitable for oral, parenteral, or nasopharyngeal delivery.

Claim 8 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated by the approved label provided as Exhibit E, LETAIRIS™ tablets are to be administered orally.

Claim 9

The composition of claim 7, wherein the composition is in a solid form.

Claim 9 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated by the approved label provided as Exhibit E, LETAIRIS™ tablets are film-coated tablets.

Claim 11

The composition of claim 7, wherein the composition is in the form of a tablet, capsule, powder, granule, suppository, solution, colloid, ointment, cream, vapor or spray.

Claim 11 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated by the approved label provided as Exhibit E, LETAIRIS™ tablets are film-coated tablets.

Claim 12

The composition of claim 7, wherein the carrier comprises a tablet binder, filler, preservative, tablet disintegrant, flow regulator, plasticizer, wetting agent, dispersant, emulsifier, solvent, release-slowing agent, antioxidant, or propellant gas.

Claim 12 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated by the approved label provided as Exhibit E, LETAIRIS™ tablets contain croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

Claim 13

The composition of claim 7, wherein the compound is an optically active enantiomer.

Claim 13 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated in the approved label provided as Exhibit E, ambrisentan contains a single chiral center determined to be in the (S) configuration.

Claim 14

The composition of claim 13, wherein the enantiomer is the S enantiomer.

Claim 14 embraces a pharmaceutical composition comprising the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. LETAIRIS™ tablets contain ambrisentan. As illustrated in the approved label provided as Exhibit E, ambrisentan is an optically active enantiomer and contains a single chiral center determined to be in the (S) configuration.

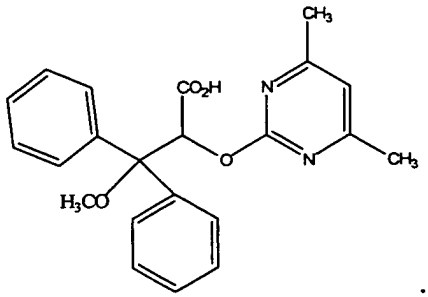
Claim 15

The composition of claim 14, wherein the enantiomer is the pure form of the S enantiomer.

Claim 15 embraces the active ingredient, ambrisentan, of the approved product, LETAIRIS™ tablets. As illustrated in the approved label provided as Exhibit E, ambrisentan contains a single chiral center determined to be in the (S) configuration.

Claim 18

The compound



Claim 18 embraces the active ingredient, ambrisentan, approved product LETAIRIS™ tablets, which contain ambrisentan. The structural formula depicted in Claim 18 embraces ambrisentan, (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid.

Therefore, as demonstrated above, Claims 1-4, 7-9, 11-15 and 18 of U.S.'205 read on the approved product, LETAIRIS™ tablets.

10. Statement of Relevant Dates to Determine the Regulatory Review Period [37 C.F.R. §1.740(a)(10)]

The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) *Patent Issue Date*

U.S.'205 was issued on **19 September 2006.**

(b) *IND Effective Date [§ 1.740(a)(10)(i)(A)]*

The INDA for the approved product, LETAIRIS™ tablets, was submitted to the FDA on 3 June 2002. A copy of the letter transmitting the INDA to the FDA is attached as Exhibit H. The FDA accorded the INDA a date of receipt of 4 June 2002, and the INDA was assigned number 64,915 ("IND 64,915"). A copy of the letter from the FDA acknowledging receipt of IND 64,915 is attached as Exhibit I. Accordingly, IND 64,915 became effective on **4 July 2002.**

(c) *NDA Submission Date [§ 1.740(a)(10)(i)(B)]*

The NDA for the approved product, LETAIRIS™ tablets, was submitted to the FDA on 13 December 2006. A copy of the letter transmitting the NDA to the FDA is attached as Exhibit B. The FDA accorded the NDA a date of receipt of 18 December 2006, and the NDA was assigned number 22-081 ("NDA 22-081"). A copy of the letter from the FDA acknowledging receipt of NDA 22-081 is attached as Exhibit J. Accordingly, NDA 22-081 became effective on **18 December 2006.**

(d) *NDA Approval Date [§ 1.740(a)(10)(i)(C)]*

NDA 22-081 was approved by the FDA on **15 June 2007.** A copy of the approval letter from the FDA to Gilead is attached as Exhibit C.

11. Brief Description of Activities Undertaken During the Regulatory Review Period [37 C.F.R. §1.740(a)(11)]

A description of significant activities undertaken by the marketing applicant, Gilead through Myogen, Inc. (now Gilead Colorado, Inc. a wholly owned subsidiary of Gilead), during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are set forth in Exhibit K. Exhibit K is divided into two parts as follows: (K-1) IND 64,915 Chronology and (K-2) NDA 22-081 Chronology.

12. Opinion of Eligibility for Extension [37 C.F.R. §1.740(a)(12)]

In the opinion of Applicant, U.S.'205 is eligible for patent term extension under the provisions of 35 U.S.C. §156. Specifically, Applicant believes that the requirements of 35 U.S.C. §156 for an extension of patent term are satisfied as follows:

(1) Patent with Eligible Subject Matter [35 U.S.C. §156(a)]

The patent has claims which embrace the active ingredient of LETAIRIS™ tablets.

(2) Non-expiration of Patent Term [35 U.S.C. §156(a)(1)]

The term of U.S.'205 expires 7 October 2015, which is 20 years from the filing date of the priority patent application. Although a patent term adjustment under 154(b) was recorded, the 7 October 2015 expiration date is maintained in order to comply with the Terminal Disclaimers provided as Exhibits G-1 to G-3. Therefore, this application has been submitted before the expiration of the patent term.

(3) No Prior Patent Term Extension [35 U.S.C. §156(a)(2)]

The term of U.S.'205 has never been extended.

(4) Owner or Agent [35 U.S.C. §156(a)(3)]

The present application for extension is submitted by the owner of record, Abbott GmbH & Co. KG in accordance with the requirements of 35 U.S.C. §156(d).

(5) Regulatory Review [35 U.S.C. §156(a)(4)]

The approved product was subject to a regulatory review period under Section 505(b)(1) of the FFDCA before its commercial marketing or use (see Exhibits B and H).

(6) First Marketing Approval [35 U.S.C. §156(a)(5)(A)]

The permission for commercial marketing of LETAIRIS™ tablets is the first permitted commercial marketing of ambrisentan.

(7) No Extension of Other Patent [35 U.S.C. §156(c)(4)]

No other patent has been extended for the same regulatory review period for the approved product, LETAIRIS™ tablets.

STATEMENT AS TO LENGTH OF EXTENSION CLAIMED

The extension period of U.S.'205, as calculated below, is **225 days** from the original patent term (7 October 2015) to **19 May 2016**.

Regulatory review period [§1.775(c)]

IND phase [§1.775(c)(1)]

The number of days in the period beginning on the date an exemption under FDCA §505(i) became effective for the approved product (4 July 2002) and ending on the date an NDA was initially submitted under FDCA §505 (18 December 2006)	1629 days

NDA phase [§ 1.775(c)(2)]

The number of days in the period beginning on the date the application was initially submitted for the approved product under FDCA §505 (18 December 2006) and ending on the date the NDA was approved (15 June 2007)	180 days

Total regulatory review period	**1809 days**

Subtractions and limitations [§1.775(d)]

Reduction for regulatory review before patent grant [§1.775(d)(1)(i)]

The number of days in the periods of §1.775(c)(1) (IND phase) and (c)(2) (NDA phase) on or before the date the patent issued (19 September 2006)	1539 days

Reduction for lack of due diligence [§1.775(d)(1)(ii)]

The number of days in the periods of §1.775(c)(1) (IND phase) and (c)(2) (NDA phase) during which the applicant did not act with due diligence	0 days

Net subtraction

One-half the number of days remaining in the period of §1.775 (c)(1) (IND phase) after the reductions above	45 days

Net preliminary term extension [§1.775(d)(1)]	**225 days**

Fourteen Year Comparison [§1.775(d)(2)-(4)]

The new expiration date of U.S.'205 with the 225 day extension determined above is 19 May 2016 which is earlier than 15 June 2021, fourteen years from the approval date of NDA 22-081 (15 June 2007).

Five Year Comparison [§1.775(d)(5)]

The 225 day extension calculated above does not exceed five years.

Accordingly, it is respectfully requested that the term of U.S.'205 be extended **225 days** from the original patent term (7 October 2015) to: **19 May 2016**.

13. Duty of Disclosure [37 C.F.R. §1.740(a)(13)]

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought, particularly as that duty is defined in 37 C.F.R. §1.765.

Applicant advises that it is concurrently filing applications under 35 U.S.C. §156 and 37 C.F.R. §1.140, based on the Regulatory Review period for LETAIRIS product, to extend terms of following patents:

-- U.S. Patent No. 5,703,017;

-- U.S. Patent No. 5,840,722;

-- U.S Patent No. 5,932,730; and

-- U.S. Patent No. 7,109,205.

Applicant will, during co-pendency of these four applications, elect one of the four applications to proceed to grant, and will withdraw the remaining three pending applications.

14. Fee Charge [37 C.F.R. §1.740(a)(14)]

The Commissioner of Patents and Trademarks is authorized to charge the prescribed $1,120.00 fee set forth in 37 C.F.R. §1.20(j) for receiving and acting upon this application for extension of patent term, together with any additional fees that may be required during the entire pendency of this application for extension of patent term, to Deposit Account No. 01-0025. A Fee Transmittal (PTO/SB/17) expressly authorizing the charging of fees to Deposit Account No. 01-0025 in this matter is being submitted in duplicate with the pending application for extension of patent term.

15. Correspondence Address [37 C.F.R. §1.740(a)(15)]

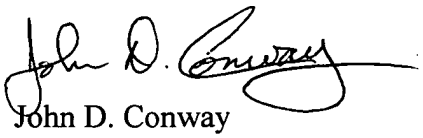
Please direct all inquiries and correspondence relating to the application for patent term extension to:

Martin L. Katz
Registration No. 25,011
Wood, Phillips, Katz, Clark & Mortimer
Citigroup Center, Suite 3800
500 West Madison Street
Chicago, IL 60661-2511

Certification under 37 C.F.R. §1.740(b)

The present application of extension of patent term for U.S.'205 is being submitted as one original and two additional copies thereof.

Respectfully submitted,

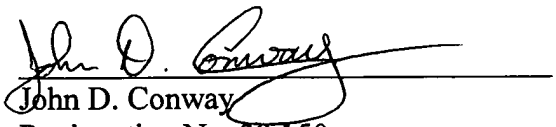


John D. Conway
Registration No. 39,150
Attorney for Applicant
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Tel.: 508-688-8046
Fax: 508-688-8110

Date: 7 August 2007

CERTIFICATE OF HAND DELIVERY

The undersigned certifies that one original and two duplicate copies of this APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 (including all Exhibits and supporting papers) are being hand-delivered this 7th day of August 2007, to "Attention: Mary C. Till, Office of Patent Legal Administration, Room MDW 7D55, 600 Dulany Street (Madison Building), Alexandria, VA 22314", United States Patent and Trademark Office.



John D. Conway
Registration No. 39,150
Attorney for Applicant
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Tel.: 508-688-8046
Fax: 508-688-8110

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 7,109,205
Title:	CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE
Issue Date:	19 September 2006
Inventors:	Hartmut Riechers, Dagmar Klinge, Wilhem Amberg, Andreas Kling, Stefan Müller, Ernst Baumann, Joachim Rheinheimer, Uwe Josef Vogelbacher, Wolfgang Wernet, Liliane Unger, and Manfred Raschack
Assignee and Owner:	Abbott GmbH & Co. KG

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156
EXHIBIT LIST

Exhibit A: Chain of Title/Ownership Recordation (Assignment)

Exhibit B: Copy of letter transmitting NDA 22-081 to the FDA

Exhibit C: FDA approval letter of NDA 22-081 to Gilead Sciences, Inc.

Exhibit D: Statement of Reliance

Exhibit E: Approved label for LETAIRIS™ tablets

Exhibit F: Copy of US Patent No. 7,109,205

Exhibit G: Post-Issuance Activity Documents
- G-1: 24 August 2005 Terminal Disclaimer (U.S. Patent No. 5,932,730)
- G-2: 24 August 2005 Terminal Disclaimer (U.S. Patent No. 6,197,958)
- G-3: 24 August 2005 Terminal Disclaimer (U.S. Patent No. 6,600,043)
- G-4: Copy of maintenance fee statement

Exhibit H: Copy of letter transmitting IND 64,915 to the FDA

Exhibit I: Copy of letter from the FDA acknowledging receipt of IND 64,915

Exhibit J: Copy of letter from the FDA acknowledging receipt of NDA 22-081

Exhibit K: Description of significant activities
K-1 IND 64,915 Chronology
K-2 NDA 22-081 Chronology

Exhibit L: Calculation of Length of Patent Term Extension for a Human Drug Product

EXHIBIT
A

US Patent 7,109,205

HDP Reference 8493-500061

Chain of Title/Ownership Recordation

1. 014778/0028 — 8 Pages
   Assignment
   Inventors to Abbott GmbH & Co. KG

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 7109205 **Issue Dt:** 09/19/2006 **Application #:** 10602275 **Filing Dt:** 06/24/2003

Publication #: 20040092742 **Pub Dt:** 05/13/2004

Inventors: Hartmut Riechers, Dagmar Klinge, Wilhelm Amberg, Andreas Kling, Stefan Muller et al

Title: NOVEL CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE

Assignment: 1

Reel/Frame: 014778/0028 **Recorded:** 12/11/2003 **Pages:** 8

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:	RIECHERS, HARTMUT	**Exec Dt:** 06/24/2003
	KLINGE, DAGMAR	**Exec Dt:** 06/24/2003
	AMBERG, WILHELM	**Exec Dt:** 06/24/2003
	KLING, ANDREAS	**Exec Dt:** 06/24/2003
	MULLER, STEFAN	**Exec Dt:** 08/12/2003
	BAUMANN, ERNST	**Exec Dt:** 08/27/2003
	RHEINHEIMER, JOACHIM	**Exec Dt:** 09/02/2003
	VOGELBACHER, UWE JOSEF	**Exec Dt:** 09/08/2003
	WERNET, WOLFGANG	**Exec Dt:** 09/29/2003
	UNGER, LILIANE	**Exec Dt:** 10/07/2003
	RASCHACK, MANFRED	**Exec Dt:** 10/12/2003

Assignee: ABBOTT GMBH & CO. KG
MAX-PLANCK-RING 2
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Correspondent: WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
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500 W. MADISON STREET
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OMB No. 0651-0027 (exp. 6/30/2005)
Tab settings ⇨ ⇨ ⇨

REC

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

To the Honorable Commissioner of Patents: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Hartmut Riechers
Dagmar Klinge
Wilhelm Amberg
Andreas Kling
Additional name(s) of conveying party(ies) attached? ☑ Yes ☐ No

2. Name and address of receiving party(ies)
Name: Abbott GmbH & Co. KG
Internal Address:
Street Address: Max-Planck-Ring 2
65205 Wiesbaden, Germany
City: State: Zip:
Additional name(s) & address(es) attached? ☐ Yes ☑ No

3. Nature of conveyance:
☑ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: 6/24/03

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s) 10/602,275
B. Patent No.(s)
Additional numbers attached? ☐ Yes ☑ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Martin L. Katz
Internal Address: Wood, Phillips, Katz, Clark & Mortimer
Street Address: 500 W. Madison Street
City: Chicago State: IL Zip: 60661

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00
☐ Enclosed
☑ Authorized to be charged to deposit account

8. Deposit account number:
23-0785

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01 FC:8021 40.00 DA

9. Signature.

Martin L. Katz
Name of Person Signing

Martin L. Katz
Signature

December 8, 2003
Date

Total number of pages including cover sheet, attachments, and documents: 9

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

25.08.03 12:15

Assignment

Serial No.: 10/602,275 Filed: June 24, 2003

In Consideration of One Dollar and other good and valuable considerations, the receipt of which is hereby acknowledged, the entire right, title and interest in the invention or improvements of the undersigned in **Novel Carboxylic Acid Derivatives, Their Preparation and Use** and in the application for Letters Patent of the United States therefor, executed by the undersigned concurrently herewith, and in any reissue or extension of any Letters Patent that may be granted upon said application are hereby assigned by the undersigned to **Abbott GmbH & CO. KG** a **Germany** corporation, having offices at **Max-Planck-Ring 2, 65205 Wiesbaden, Germany** and the heirs, successors, legal representatives and assigns of **Abbott GmbH & CO. KG** (hereinafter collectively called said Assignee), and the Commissioner of Patents and Trademarks is hereby authorized and requested by the undersigned to issue said Letters Patent to said Assignee.

For said considerations it is hereby agreed by the undersigned, upon the request of said Assignee, to execute any necessary and proper oaths or affidavits relating to said application or required for the filing or prosecution of any divisional or continuing application thereof or for the filing or prosecution of any application for the reissue or extension of any Letters Patent that may be granted on said invention or improvements that said Assignee may deem necessary or expedient, and for the said considerations it is further agreed by the undersigned, upon the request of said Assignee, in the event of said application or any division thereof, or Letters Patent issued thereon, or any reissue or application for the reissue thereof, becoming involved in Interference, to cooperate to the best of the ability of the undersigned with said Assignee in the matters of preparing and executing the preliminary statement and giving and producing evidence in support thereof, and further to perform, upon such request, any and all affirmative acts to obtain said Letters Patent and vest all rights therein hereby conveyed in the said Assignee as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment and sale had not been made. And for the said considerations the entire right, title and interest in said invention or improvements, including all priority rights, and the right to claim priority rights and the privileges and benefits thereof, including those under the International Convention, and all other Conventions, and the right to file applications for patent in said Assignee's own name for said invention or improvements in each and every country of the world are hereby assigned and granted by the undersigned to said Assignee. It is further agreed by the undersigned, upon the request of said Assignee, to execute any and all documents that shall be required of the undersigned to be executed in connection with any and all applications for foreign Letters Patent therefor, including the prosecution thereof, and to execute any and all documents necessary to invest title in said foreign applications and patents in said Assignee. The undersigned also further agrees, for the said considerations, upon the request of said Assignee, to promptly perform all lawful acts deemed by said Assignee to be necessary or advisable in connection with maintaining, enforcing, or transferring the resulting grants of said Letters Patent in the United States or foreign countries. It is agreed that such lawful acts include, but are not limited to, taking oaths, executing declarations, powers, assignments and other papers and giving testimony.

Serial No.: 10/602,275 Filed: June 24, 2003

The attorneys of record in such application for patent are hereby authorized and requested by the undersigned to insert in this Assignment the date and serial number thereof in the places provided therefor.

Hartmut Riechers

Executed this 29th day of July, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Hartmut Riechers appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires: _____

* * * * *

Dagmar Klinge

Executed this 7th day of August, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Dagmar Klinge appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires: _____

* * * * *

Serial No.: 10/602,275 Filed: June 24, 2003

Wilhelm Amberg

Executed this 15th day of September, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Wilhelm Amberg appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) Notary Public

My Commission Expires: _____

* * * * *

Andreas Kling

Executed this 12th day of September, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Andreas Kling appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) Notary Public

My Commission Expires: _____

* * * * *

Stefan Muller

Executed this 12th day of August, 2003.

Serial No.: 10/602,275 Filed: June 24, 2003

State of_____)
) ss.
County of_____)

On _____, 2003, Stefan Muller appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires:_____

* * * * *

_____
Ernst Baumann

Executed this 23rd day of August, 2003.

State of_____)
) ss.
County of_____)

On _____, 2003, Ernst Baumann appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assigument for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires:_____

* * * * *

_____
Joachim Rheinheimer

Executed this 22nd day of September, 2003.

State of_____)
) ss.

Serial No.: 10/602,275 Filed: June 24, 2003

County of_____)

On _____, 2003, Joachim Rheinheimer appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires:_____

* * * * *

Uwe Josef Vogelbacher

Executed this 8th day of September, 2003.

State of_____)
) ss.
County of_____)

On _____, 2003, Uwe Josef Vogelbacher appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires:_____

* * * * *

Wolfgang Wernet

Executed this 29th day of September, 2003.

State of_____)
) ss.
County of_____)

Serial No.: 10/602,275 Filed: June 24, 2003

On _____, 2003, Wolfgang Wernet appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires: _____

* * * * *

_____
Liliane Unger

Executed this 7 day of October, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Liliane Unger appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

(SEAL) _____
Notary Public

My Commission Expires: _____

* * * * *

_____
Manfred Raschack

Executed this 12 day of October, 2003.

State of _____)
) ss.
County of _____)

On _____, 2003, Manfred Raschack appeared before me, a Notary Public, in and for the State and County aforesaid, and acknowledged that he/she freely and voluntarily subscribed and executed the foregoing Assignment for the purposes and uses therein expressed.

Serial No.: 10/602,275 Filed: June 24, 2003

(SEAL)

Notary Public

My Commission Expires:

EXHIBIT
B

Advancing Therapeutics.
Improving Lives.

Linnea Tanner
Director, Regulatory Affairs

13 December 2006

Norman L. Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Subject: **NDA 22-081 (022081-0000)** **NEW DRUG APPLICATION**
LETAIRIS™ (ambrisentan) Tablets Original Submission

Dear Dr. Stockbridge:

Pursuant to the Paragraph 505(b)(1) of the Federal, Food, Drug and Cosmetic Act (the ACT) and 21 CFR 314.50, Gilead Sciences, Inc. (Gilead) hereby submits a New Drug Application (NDA) for LETAIRIS (ambrisentan) Tablets, 5 and 10 mg. Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening and improve symptoms.

Myogen, Inc. was acquired by Gilead Sciences, Inc. and became a wholly owned subsidiary known as Gilead Colorado, Inc., effective November 17, 2006. Thus, the NDA applicant is Gilead Sciences, Inc., which assumes all the responsibilities and obligations of the NDA. However, the name Myogen, Inc. is used throughout the NDA for historical reasons and because of the timing of acquisition.

Request for Priority Review

Ambrisentan was granted Fast Track designation for the treatment of pulmonary arterial hypertension (PAH) on February 15, 2006; therefore, we request that this application be given priority review. PAH is a rare, serious and life-threatening disease for which there is no cure. Although there are other therapies currently approved for this disease, there still is an unmet medical need for the treatment of PAH. LETAIRIS is an alternative, therapeutic option for these patients that has the potential to provide significant benefit over currently authorized therapies for the following reasons:

- Improved effects on exercise capacity, an efficacy measure that has been shown to correlate with and be prognostic of long-term survival
- Significant delay of the clinical worsening of PAH, an efficacy measure of disease progression in this ultimately fatal disease
- Improved effects on symptoms associated with PAH (WHO functional class, Borg dyspnea index, and SF-36® physical function scale)
- Low incidence of liver function test (LFT) abnormalities, a serious toxicity that can lead to discontinuation of treatment with other ERA therapies
- Potential to provide benefit to PAH patients who have previously discontinued ERA therapy due to LFT abnormalities
- No clinically significant cytochrome P450 (CYP) enzyme-related interactions with several drugs that are currently contraindicated, less effective, or associated with significant safety issues when co-administered with other PAH therapies

Orphan Drug Designation

Ambrisentan was granted orphan drug designation (Designation Request #04-1836) for the treatment of PAH and, therefore, qualifies for seven (7) years of exclusive marketing rights pursuant to Section 527 of the ACT (21 U.S.C. 360 cc). A letter dated December 07, 2006 was submitted to the Office of Orphan Drug Products Development to transfer the orphan designation from Myogen, Inc. to Gilead Sciences, Inc.

Application Fee

Under Section 736(a)(1)(E) of the ACT, this NDA is not subject to an application fee because LETAIRIS (ambrisentan) Tablets, 5 and 10 mg, is indicated for the treatment of a rare disease or condition designated under Section 526 of the ACT (orphan drug designation).

Pediatric Data

Since ambrisentan was granted orphan designation for PAH under Section 526 of the ACT (21 U.S.C. 360bb), no pediatric data is submitted in the original NDA 22-081. Pediatric data is not required for applications to market the product for the orphan-designated indications and a waiver is not needed [21 CFR 314.55(d) for NDAs and 601.27(d) for BLAs]. As agreed during the Pre-NDA meeting on May 19, 2006, Gilead will submit a pediatric study request and a proposal for a pediatric study following the NDA submission so that the Division can issue a written request to initiate pediatric studies that will be used to support pediatric exclusivity.

Proposed Proprietary Name

The proposed proprietary name of LETAIRIS was submitted for review on November 4, 2005 in Serial No. 094 of IND 64,915.

Application Format

The archive copy of NDA 22-081 (eCTD 022081-0000) is provided in its entirety as an electronic submission using the electronic Common Technical Document (eCTD) format in accordance with the guidance *M2: eCTD: Electronic Common Technical Document Specification* and as agreed in the Pre-NDA meeting on May 19, 2006. Gilead has notified the FDA Denver District office about the NDA submission in the eCTD format. A copy of the field copy certification is provided in Section m1.3.2.

Please refer to an attachment (Summary of FDA Interactions and Commitments for Ambrisentan Development Plan) to this cover letter for any other agreements of the format and content of the NDA, including the electronic datasets.

Required Regulatory Forms applicable to this submission have been included in the electronic submission and are signed electronically. Pursuant to 21 CFR 11.100, Gilead certifies that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

This submission is provided on a DVD-ROM and is approximately 4.2 GB. Gilead certifies that the submission is virus free as defined by the 11 December 2006 version of the McAfee® VirusScan® Enterprise-program, Version 8.0.0, Scan Engine 5100, with 4916 virus definitions.

Annotated ECG Waveform Data

In accordance with the instructions available on the CDER Electronic Regulatory Submissions and Review website, and confirmation with the Office of Business Process Support (OBPS), Gilead has submitted annotated ECG waveform data in XML format to the E-Scribe ECG Warehouse. These files are representative of data collected in a Phase 1 QTc study (AMB-104), and the two pivotal Phase 3 studies (AMB-320 and AMB-321). These data files are now available for your review through E-Scribe ECG Warehouse.

Contact Information

Regulatory Contact:
Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westmister, CO 80021-5426
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Regulatory Contact - CMC:
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Associate Director, CMC Regulatory
Gilead Colorado, Inc.
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Westmister, CO 80021-5426
Phone (direct): 303-464-3958
Facsimile: 303-410-3354
e-mail: todd.marshall@gilead.com

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Westmister, CO 80021-5426
Phone (direct): 303-410-3206
Facsimile: 303-410-3354
e-mail: liam.curran@gilead.com

Please do not hesitate to contact me with any questions.

Sincerely,

{See appended electronic signature page}

Linnea Tanner
Director, Regulatory Affairs
Phone: 303-410-3243
Fax: 303-410-3354

Attachment: Summary of FDA Interactions and Commitments for Ambrisentan Development Plan

Document Approval Certificate

THE PRECEDING DOCUMENT HAS BEEN ELECTRONICALLY SIGNED BY:

UserName: ltanner
Title: Director, Regulatory Affairs
Date: Wednesday, 13 December 2006, 05:30 PM Mountain Daylight Time
Meaning: Document approved and signed

EXHIBIT
C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Sciences, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado
7575 West 103rd Ave., Suite #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

Please refer to your new drug application (NDA) dated December 13, 2006 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We acknowledge receipt of your submission(s) dated January 11 and 26, February 28, March 2, 13, 16, and 26, April 6, 17, and 24, May 1, 11, 14, 15, and 30, and June 1, 6, and 11, 2007.

This new drug application provides for the use of Letairis (ambrisentan) 5 and 10 mg Tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

We have completed our review of this application. It is approved with restrictions to assure safe use under the provisions of the Subpart H regulations (21 CFR 314.520), effective on the date of this letter, for use as recommended in the enclosed labeling text, Medication Guide, RiskMAP, and carton and container labels. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced restricted distribution approval regulations.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, RiskMAP, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-081**." Approval of this submission by FDA is not required before the labeling is used.

The Pediatric Research Equity Act is not applicable to drugs granted orphan drug designation.

The postmarketing study commitments that have been agreed upon based on your written correspondence dated 6/15/07 are listed below:

1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at peak and trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.
   Protocol Submission: by 10/1/2007
   Study Start: by 06/2008
   Final Report Submission: by 12/2009

2. Gilead agrees to submit the results of the Phase 1 ketoconazole drug interaction study that has already been completed.
   Final Report Submission: by 10/2007

3. Gilead agrees to a post-approval commitment to explore the interaction potential of strong inhibitors of CYP2C19 (e.g. omeprazole) on ambrisentan pharmacokinetics in humans. Gilead further agrees to explore the interaction potential of cyclosporine A (strong inhibitor of OATP and P-gp) and rifampin (inhibitor of OATP and inducer of P-gp, CYPs 3A and 2C19) on ambrisentan pharmacokinetics in humans.
   Protocol Submission: by 10/1/2007
   Study Start: by 04/2008
   Final Report Submission: by 12/2008
   This commitment might also be addressed by analysis of existing data.

4. With regard to the RiskMAP, Gilead agrees to submit to the FDA by July 15, 2007, the following documents:
   i. The pregnancy exposure root cause analysis plan including the questionnaire that will be used in the analysis plan;
   ii. The patient and prescriber knowledge, attitude, and behavior survey tools for the RiskMAP evaluation plan;
   iii. The Pharmacy Standard Operating Procedures (SOPs); and
   iv. The Pharmacy Audit Plan.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have determined that Letairis poses a serious and significant public health concern relating to women of child-bearing potential and patients with liver impairment. This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of

information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Letairis. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Letairis that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, PharmD, MBA, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
6/15/2007 04:56:32 PM

EXHIBIT
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GILEAD
Advancing Therapeutics.
Improving Lives.

LETTER OF RELIANCE

Mail Stop **Hatch-Waxman PTE**
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Attn: Mary C. Till, Examiner
Office of Patent Legal Administration

Gilead Sciences, Inc., Licensee of the exclusive rights to U.S. Patent No. 7,109,205 ("U.S.'205"), authorizes **Abbott Laboratories**, Licensor and record-owner of U.S.'205, to rely on the activities of Gilead Sciences, Inc. supporting FDA approval of LETAIRIS™ (ambrisentan) product (5 and 10 mg tablets), for the purpose of obtaining extension of patent term of U.S.'205, as provided under 35 U.S.C. §156(d)(1), 37 C.F.R. §1.730 and MPEP 2752.

Date: 8/2/07

Authorized by Gilead Sciences, Inc.

By: Richard J. Gorczynski

Richard J. Gorczynski, PhD
SVP, Cardiovascular Therapeutics

Gilead Colorado, Inc. 7575 West 103rd Ave. #102 Westminster, CO 80021
phone 303-410-6666 *facsimile* 303-410-6667
www.gilead.com

EXHIBIT
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LETAIRIS™ tablets safely and effectively. See full prescribing information for LETAIRIS.

LETAIRIS (ambrisentan) tablets for oral use
Initial U.S. Approval: 2007

WARNING: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

See full prescribing information for complete boxed warning.

- **Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs.**
- **Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN or by signs or symptoms of liver dysfunction.**
- **May cause fetal harm if taken during pregnancy (4.1)**
- **Must exclude pregnancy before the start of treatment (2.2)**
- **Prevent pregnancy thereafter by the use of two reliable methods of contraception (2.2)**

----------INDICATIONS AND USAGE----------

LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening (1).

----------DOSAGE AND ADMINISTRATION----------

- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated (2.1).
- Treat women of child-bearing potential only after a negative pregnancy test and treat only women who are using two reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted. Obtain monthly pregnancy tests (2.2).
- Not recommended in patients with moderate or severe hepatic impairment (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 5 mg and 10mg film-coated, unscored tablets (3)

----------CONTRAINDICATIONS----------

- Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm (4.1).

----------WARNINGS AND PRECAUTIONS----------

- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.2).
- Mild to moderate peripheral edema (5.3)
- Use caution when LETAIRIS is co-administered with cyclosporine A (5.4 and 7).
- Use caution when LETAIRIS is co-administered with strong CYP3A and 2C19 inhibitors (5.5 and 7).

----------ADVERSE REACTIONS----------

Most common placebo-adjusted adverse reactions are peripheral edema, nasal congestion, sinusitis, flushing, palpitations, abdominal pain, and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at (1-800-GILEAD5, Option 3) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- No significant interactions of LETAIRIS with warfarin or sildenafil have been observed (7).
- Other potential interactions are not well characterized, but, based on *in vitro* data, interactions with P-glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4,and CYP2C19 inhibitors, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) would be expected (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy Category X: LETAIRIS is contraindicated in pregnant women (4.1 and 8.1).
- Nursing mothers: Breastfeeding while receiving LETAIRIS is not recommended (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide)

Revised: [06/2007]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3 x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2 x ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals *[see Contraindications (4.1)]*. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNg 20 IUD inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests.

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP *[see WARNINGS, Prescribing and Distribution Program for LETAIRIS]*.

1 INDICATIONS AND USAGE

LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). Liver function tests should be measured prior to initiation and during treatment with LETAIRIS *[see Warnings and Precautions (5.1)]*.

2.2 Women of Childbearing Potential

Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted. In those cases, no other contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS *[see Contraindications (4.1)]*.

2.3 Pre-existing Hepatic Impairment

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment *[see Special Populations (8.7)]*. Use caution in patients with mild hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS

LETAIRIS is available as 5 mg and 10 mg film-coated, unscored tablets.

4 CONTRAINDICATIONS

4.1 Pregnancy Category X

LETAIRIS may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of ≥15 mg/kg/day in rats and ≥7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women.

LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of two reliable methods of contraception *[see Dosage and Administration (2.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential Liver Injury (see BOXED WARNING)

Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3-times the upper limit of normal (>3 x ULN) and total bilirubin >2 x ULN is a marker for potentially serious hepatic injury.

Liver function tests were closely monitored in all clinical studies with LETAIRIS. For all LETAIRIS-treated patients (N=483), the 12-week incidence of aminotransferases >3 x ULN was 0.8% and >8 x ULN was 0.2%. For placebo-treated patients, the 12-week incidence of aminotransferases >3 x ULN was 2.3% and >8 x ULN was 0.0%. The 1-year rate of aminotransferase elevations >3 x ULN with LETAIRIS was 2.8% and >8 x ULN was 0.5%. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN.

Liver chemistries must be measured prior to initiation of LETAIRIS and at least every month thereafter. If there are aminotransferase elevations >3 x ULN and ≤5 x ULN, they should be re-measured. If the confirmed level is >3 x ULN and ≤5 x ULN, reduce the daily dose or interrupt treatment and continue to monitor every two weeks until the levels are <3 x ULN. If there are aminotransferase elevations >5 x ULN and ≤8 x ULN, LETAIRIS should be discontinued and monitoring should continue until the levels are <3 x ULN. LETAIRIS can then be re-initiated with more frequent measurement of aminotransferase levels. If there are aminotransferase elevations >8 x ULN, treatment should be stopped and re-initiation should not be considered.

LETAIRIS is not recommended in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin >2 x ULN, LETAIRIS treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

5.2 Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETAIRIS in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving LETAIRIS (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo.

The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at one month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

5.3 Peripheral Edema

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo *[see Adverse Reactions (6)]*. Most edema was mild to moderate in severity. If clinically significant peripheral edema develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as heart failure, and the possible need for specific treatment.

5.4 Co-administration of LETAIRIS and Cyclosporine A

Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), Organic Anion Transport Protein (OATP), and CYP3A4. *In vitro* data indicate ambrisentan is a substrate of P-gp, OATP and CYP3A. Therefore, use caution when LETAIRIS is co-administered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS *[see Drug Interactions (7)]*.

5.5 Co-administration of LETAIRIS and Strong CYP3A and 2C19 Inhibitors

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) and CYP2C19-inhibitors (e.g., omeprazole) *[see Drug Interactions (7)]*.

5.6 Prescribing and Distribution Program for LETAIRIS

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

To enroll in LEAP, prescribers must complete the LEAP Prescriber Enrollment and Agreement Form indicating agreement to (see LEAP Prescriber Enrollment and Agreement Form for full prescribing physician agreement):

- Read the Prescribing Information (PI) and Medication Guide for LETAIRIS
- Enroll all patients in LEAP and re-enroll patients after the first 6 months of treatment and annually thereafter
- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient

- Educate patients on the risks of LETAIRIS, including the risks of hepatotoxicity and teratogenicity *[see Boxed Warning]*
- Educate and counsel women of childbearing potential to use two different forms of contraception including at least one primary form during LETAIRIS treatment and for one month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed *[see Boxed Warning, Contraindication (4.1)]*.

  Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization.

  Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- Order and review liver function tests (including aminotransferases and bilirubin) prior to initiation of LETAIRIS treatment and monthly during treatment
- For women of childbearing potential, order and review a pregnancy test prior to initiation of LETAIRIS treatment and monthly during treatment
- Counsel patients who fail to comply with the program requirements
- Notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for LETAIRIS were obtained from two 12-week, placebo-controlled studies in patients with PAH (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse events that occurred in >3% of the patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

Table 1 Adverse Events in >3% of PAH Patients Receiving LETAIRIS and More Frequent than Placebo

	Placebo (N=132)	LETAIRIS (N=261)	
Adverse event	**n (%)**	**n (%)**	**Placebo-adjusted (%)**
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3
Palpitations	3 (2)	12 (5)	3
Nasopharyngitis	1 (1)	9 (3)	2
Abdominal pain	1 (1)	8 (3)	2
Constipation	2 (2)	10 (4)	2
Dyspnea	4 (3)	11 (4)	1
Headache	18 (14)	38 (15)	1

Note: This table includes all adverse events >3% incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of ≥1% between the LETAIRIS and placebo groups.

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Fewer patients receiving LETAIRIS had adverse events related to liver function tests compared to placebo.

Few notable differences in the incidence of adverse drug reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients).

7 DRUG INTERACTIONS

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of Organic Anion Transport Protein (OATP). *In vitro* studies show ambrisentan is a substrate but not an inhibitor of P-gp.

The drug interaction potential of ambrisentan is not well characterized because *in vivo* drug interaction studies were not conducted with the following types of drugs: strong inhibitors of CYP3A4 (atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), and CYP2C19 (omeprazole), strong inducers of CYP3A and 2C19 (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin); and inducers of CYPs, UGTs and P-gp (rifampin). The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown.

7.1 Cyclosporine A

Use caution when LETAIRIS is co-administered with cyclosporine A (see Warnings and Precautions 5.4).

7.2 Strong CYP3A or 2C19 Inhibitors

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole) *[see Warnings and Precautions (5.5)]*.

7.3 Inducers of P-gp, CYPs, and UGTs

Use caution when LETAIRIS is co-administered with inducers of P-gp, CYPs, and UGTs.

7.4 Warfarin

In healthy volunteers receiving warfarin, daily doses of LETAIRIS (10 mg once daily) did not have a clinically significant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate).

In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of LETAIRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose. Therefore, no dose-adjustments for warfarin or LETAIRIS are required when co-administered.

7.5 Sildenafil

In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of LETAIRIS (10 mg once daily) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of LETAIRIS (10 mg). Therefore, no dose-adjustments for sildenafil or LETAIRIS are required when co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)]*.

8.3 Nursing Mothers

It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/mm^2 basis.

8.4 Pediatric Use

Safety and effectiveness of LETAIRIS in pediatric patients have not been established.

8.5 Geriatric Use

In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan *[see Clinical Pharmacology (12.3)]*. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment.

The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

8.7 Hepatic Impairment

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan *[see Clinical Pharmacology (12.3)]*. LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. Use caution when administering LETAIRIS to patients with mild pre-existing impaired liver function who may require reduced doses of LETAIRIS *[see Dosage and Administration (2.3)]*.

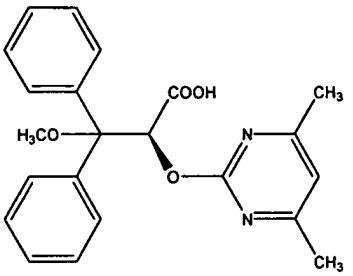
10 OVERDOSAGE

There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. Massive overdosage could potentially result in hypotension that may require intervention.

11 DESCRIPTION

LETAIRIS is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ET_A) receptor. The chemical name of ambrisentan is (+)-(2*S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. It has a molecular formula of $C_{22}H_{22}N_2O_4$ and a molecular weight of 378.42. It contains a single chiral center determined to be the (*S*) configuration and has the following structural formula:

Figure 1 Ambrisentan Structural Formula



Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

LETAIRIS is available as 5 mg and 10 mg film-coated tablets for once-daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink LETAIRIS tablet contains 5 mg of ambrisentan. Each oval, deep pink LETAIRIS tablet contains 10 mg of ambrisentan. LETAIRIS tablets are unscored.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET_A are vasoconstriction and cell proliferation, while the predominant actions of ET_B are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high affinity (K_i=0.011 nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (>4000-fold). The clinical impact of high selectivity for ET_A is not known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either LETAIRIS 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. LETAIRIS 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of LETAIRIS increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving LETAIRIS 5-10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

12.3 Pharmacokinetics

The absolute bioavailability of ambrisentan is not known. Ambrisentan is rapidly absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. *In vitro* studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. Based on *in vitro* data, interactions with strong inhibitors of P glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4, CYP2C19, and uridine 5' diphosphate glucuronosyltransferases (UGTs) are possible *[see Drug Interactions (7)]*. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and at 50, 150 and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects on survival. The high dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were

taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

Positive findings of clastogenicity were detected, at drug concentrations producing moderate to high toxicity, in the chromosome aberration assay in cultured human lymphocytes. There was no evidence for genetic toxicity of ambrisentan when tested *in vitro* in bacteria (Ames test) or *in vivo* in rats (micronucleus assay, unscheduled DNA synthesis assay).

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses ≥10 mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses ≥50 mg/kg/day (28-fold MRHD). Effects on sperm count, sperm morphology, mating performance and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). At doses of ≥10 mg/kg/day, observations of testicular histopathology in the absence of fertility and sperm effects were also present. There are insufficient data on the effects of ambrisentan or other endothelin receptor antagonists on testicular function in man.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (PAH)

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted in 393 patients with PAH (WHO Group 1). The two studies were identical in design except for the doses of LETAIRIS and the geographic region of the investigational sites. ARIES-1 compared once-daily doses of 5 mg and 10 mg LETAIRIS to placebo, while ARIES-2 compared once-daily doses of 2.5 mg and 5 mg LETAIRIS to placebo. In both studies, LETAIRIS or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, or sildenafil. The primary study endpoint was 6-minute walk distance. In addition, clinical worsening, WHO functional class, dyspnea, and SF-36® Health Survey were assessed.

Patients had idiopathic PAH (64%) or PAH associated with connective tissue disease (32%), HIV infection (3%), or anorexigen use (1%). There were no patients with PAH associated with congenital heart disease.

Patients had WHO functional class I (2%), II (38%), III (55%), or IV (5%) symptoms at baseline. The mean age of patients was 50 years, 79% of patients were female, and 77% were Caucasian.

Submaximal Exercise Capacity

Results of the 6-minute walk distance at 12 weeks for the ARIES-1 and ARIES-2 studies are shown in Table 2 and Figure 2.

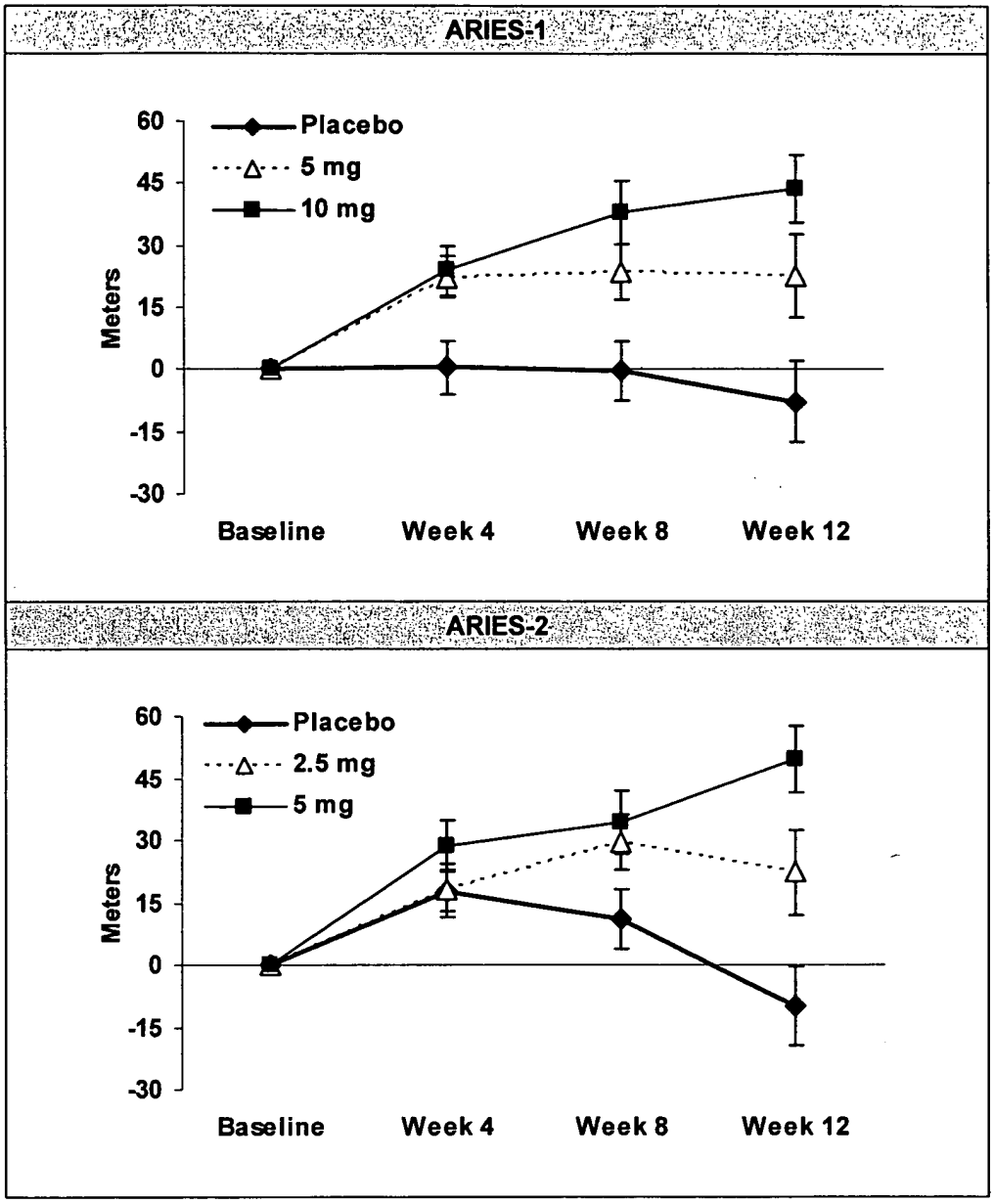
Table 2 Changes from Baseline in 6-Minute Walk Distance (meters)

	ARIES-1			ARIES-2		
	Placebo (N=67)	**5 mg (N=67)**	**10 mg (N=67)**	**Placebo (N=65)**	**2.5 mg (N=64)**	**5 mg (N=63)**
Baseline	342 ± 73	340± 77	342 ± 78	343 ± 86	347± 84	355 ± 84
Mean change from baseline	-8 ± 79	23 ± 83	44 ± 63	-10 ± 94	22 ± 83	49 ± 75
Placebo-adjusted mean change from baseline		31	51		32	59
Placebo-adjusted median change from baseline		27	39		30	45
p-value†		0.008	<0.001		0.022	<0.001

Mean ± standard deviation

† p-values are Wilcoxon rank sum test comparisons of LETAIRIS to placebo at Week 12 stratified by idiopathic PAH and non-idiopathic PAH patients

Figure 2 Mean Change in 6-minute Walk Distance



Mean change from baseline in 6-minute walk distance in the placebo and LETAIRIS groups
Values are expressed as mean ± standard error of the mean.

In both studies, treatment with LETAIRIS resulted in a significant improvement in 6-minute walk distance for each dose of LETAIRIS and the improvements increased with dose. An increase in 6-minute walk distance was observed after 4 weeks of treatment with LETAIRIS, with a dose-response observed after 12 weeks of treatment. Improvements in walk distance with LETAIRIS were smaller for elderly patients (age ≥65) than younger patients and for patients with secondary PAH than for patients

with idiopathic PAH. The results of such subgroup analyses must be interpreted cautiously.

The effects of LETAIRIS on walk distances at trough drug levels are not known. Because only once daily dosing was studied in the clinical trials, the efficacy and safety of more frequent dosing regimens for LETAIRIS are not known. If exercise capacity is not sustained throughout the day in a patient, consider other PAH treatments that have been studied with more frequent dosing regimens.

Clinical Worsening

Time to clinical worsening of PAH was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents or study withdrawal due to early escape. Early escape was defined as meeting two or more of the following criteria: a 20% decrease in the 6-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. The clinical worsening events during the 12-week treatment period of the LETAIRIS clinical trials are shown in Table 3 and Figure 3.

Table 3 Time to Clinical Worsening

	ARIES-1		ARIES-2	
	Placebo (N=67)	**LETAIRIS (N=134)**	**Placebo (N=65)**	**LETAIRIS (N=127)**
Clinical worsening, no. (%)	7 (10%)	4 (3%)	13 (22%)	8 (6%)
Hazard ratio		0.28		0.30
p-value, Fisher exact test		0.044		0.006
p-value, Log-rank test		0.030		0.005

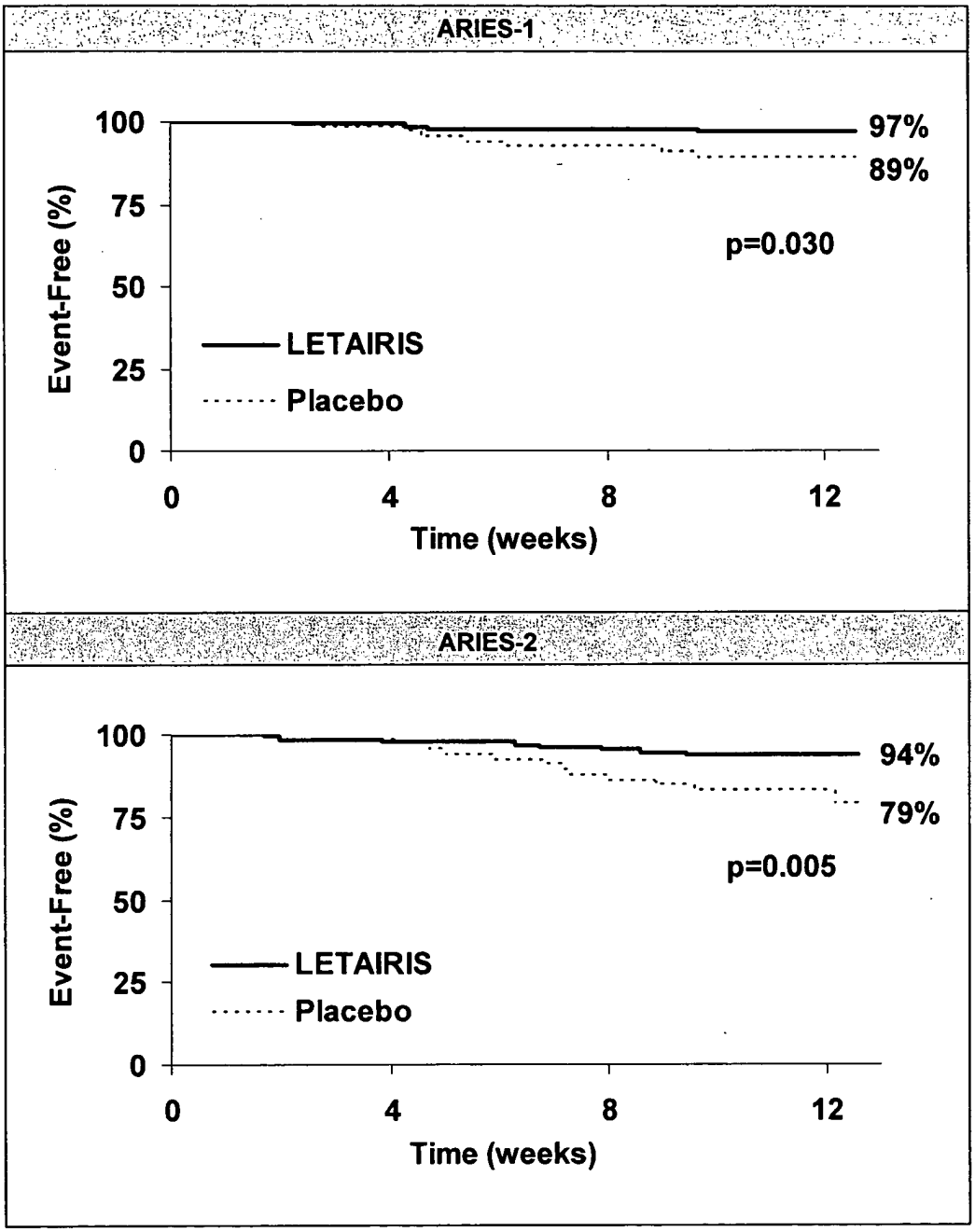
Intention-to-treat population

Note: Patients may have had more than one reason for clinical worsening.

Nominal p-values

There was a significant delay in the time to clinical worsening for patients receiving LETAIRIS compared to placebo. Results in subgroups such as the elderly were also favorable.

Figure 3 Time to Clinical Worsening



Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of failures in ARIES-1 and ARIES-2.

p-values shown are the log-rank comparisons of LETAIRIS to placebo stratified by idiopathic PAH and non-idiopathic PAH patients

14.2 Long-term Treatment of PAH

The long-term follow-up of the patients who were treated with LETAIRIS in the two pivotal studies and their open-label extension (N=383) shows that 95% were still alive at one year and 94% were still receiving LETAIRIS monotherapy. These uncontrolled observations do not allow comparison with a group not given LETAIRIS and cannot be used to determine the long-term effect of LETAIRIS.

14.3 Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x upper limit of normal (ULN) were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

16 HOW SUPPLIED/STORAGE AND HANDLING

Because of the risk of liver injury and birth defects, LETAIRIS may be prescribed only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com. Adverse events can also be reported directly via this number.

LETAIRIS film-coated, unscored tablets are supplied as follows:

Package Configuration	Tablet Strength	NDC No.	Description of Tablet; Debossed on Tablet; Size
30 count blister	5 mg	61958-0801-2	Square convex, pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square
30 count blister	10 mg	61958-0802-2	Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval

℞ only

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) *[see USP controlled room temperature]*. Store LETAIRIS in its original packaging.

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, doctors must review the LETAIRIS Medication Guide with every patient *[see FDA-Approved Medication Guide (17.5)]*.

17.1 Importance of Preventing Pregnancy

Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test. Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use two different forms of contraception including at least one primary form simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. Primary forms of contraception other than tubal sterilization include hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant *[see Prescribing and Distribution Program for LETAIRIS (5.5)]*.

17.2 Adverse Liver Effects

Patients should be advised of the importance of monthly liver function testing and instructed to immediately report any symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) to their physician.

17.3 Hematological Change

Patients should be advised of the importance of hemoglobin testing.

17.4 Administration

Patients should be advised not to split, crush, or chew tablets.

17.5 FDA-Approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

GS22-081-000

Medication Guide
LETAIRIS™ (le-TAIR-is)
Tablets
(ambrisentan)

Read this Medication Guide before you start taking LETAIRIS and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about LETAIRIS?

- **Possible liver injury.**

  LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See "What are the possible side effects of LETAIRIS?" for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

- **Serious birth defects.**

  LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment. Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

  Women who are able to get pregnant must use two different reliable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS, you must talk to your doctor, understand the benefits and risks of LETAIRIS, and agree to all of the instructions in the LEAP program.

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

Who should not take LETAIRIS?

Do not take LETAIRIS if:

- **you are pregnant, plan to become pregnant, or become pregnant during treatment with LETAIRIS. LETAIRIS can cause serious birth defects.** (See "What is the most important information I should know about LETAIRIS?") Serious birth defects from LETAIRIS happen early in pregnancy.
- **your blood tests show possible liver injury.**

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. LETAIRIS and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

LETAIRIS has not been studied in children.

How should I take LETAIRIS?

LETAIRIS will be mailed to you by a specialty pharmacy. Your doctor will give you complete details.

- Take LETAIRIS exactly as your doctor tells you. Do not stop taking LETAIRIS unless your doctor tells you.
- You can take LETAIRIS with or without food.
- Do not split, crush or chew LETAIRIS tablets.
- It will be easier to remember to take LETAIRIS if you take it at the same time each day.
- If you take more than your regular dose of LETAIRIS, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

What should I avoid while taking LETAIRIS?

- **Do not get pregnant** while taking LETAIRIS. (See the serious birth defects section of "What is the most important information I should know about LETAIRIS?") If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **Breastfeeding is not recommended** while taking LETAIRIS. It is not known if LETAIRIS can pass through your milk and harm your baby.

What are the possible side effects of LETAIRIS?

Serious side effects of LETAIRIS include:

- **Possible liver injury.** (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, right upper stomach pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

How should I store LETAIRIS?

Store LETAIRIS at less than 86 °F (30 °C), in the package it comes in.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS

for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

Call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com for more information.

What are the ingredients in LETAIRIS?

Active ingredient: ambrisentan

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

This medication guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

GS22-081-000

EXHIBIT
F

US007109205B2

(12) **United States Patent**
Riechers et al.

(10) **Patent No.: US 7,109,205 B2**
(45) **Date of Patent: Sep. 19, 2006**

(54) **CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE**

(75) Inventors: **Hartmut Riechers**, Neustadt (DE); **Dagmar Klinge**, Heidelberg (DE); **Wilhelm Amberg**, Friedrichsdorf (DE); **Andreas Kling**, Mannheim (DE); **Stefan Müller**, Speyer (DE); **Ernst Baumann**, Dudenhofen (DE); **Joachim Rheinheimer**, Ludwigshafen (DE); **Uwe Josef Vogelbacher**, Ludwigshafen (DE); **Wolfgang Wernet**, Hassloch (DE); **Liliane Unger**, Ludwigshafen (DE); **Manfred Raschack**, Weisenheim (DE)

(73) Assignee: **Abbott GmbH & Co. KG**, Wiesbaden (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 261 days.

(21) Appl. No.: **10/602,275**

(22) Filed: **Jun. 24, 2003**

(65) **Prior Publication Data**

US 2004/0092742 A1 May 13, 2004

Related U.S. Application Data

(60) Continuation of application No. 09/748,184, filed on Dec. 27, 2000, now Pat. No. 6,600,043, which is a division of application No. 09/309,770, filed on May 11, 1999, now Pat. No. 6,197,958, which is a division of application No. 09/184,152, filed on Nov. 2, 1998, now Pat. No. 5,969,134, which is a division of application No. 08/809,699, filed as application No. PCT/EP95/03903 on Oct. 7, 1995, now Pat. No. 5,932,730.

(30) **Foreign Application Priority Data**

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Sep. 7, 1995 (DE) 195 33 023

(51) **Int. Cl.**
C07D 239/02 (2006.01)
A61K 31/505 (2006.01)

(52) **U.S. Cl.** **514/274**; 544/302; 544/315; 544/318

(58) **Field of Classification Search** 544/302, 544/315, 318; 514/274
See application file for complete search history.

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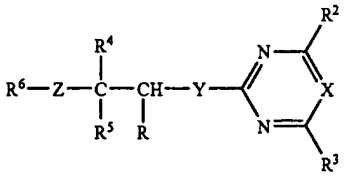
(Continued)

Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Wood, Phillips, Katz, Clark & Mortimer

(57) **ABSTRACT**

Carboxylic acid derivatives



where R–R^6, X, Y and Z have the meanings stated in the description, and the preparation thereof, are described. The novel compounds are suitable for controlling diseases.

18 Claims, No Drawings

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CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 09/748,184, filed Dec. 27, 2000, now U.S. Pat. No. 6,600,043, which is a division of application Ser. No. 09/309,770, filed May 11, 1999, now U.S. Pat. No. 6,197,958; which is a division of application Ser. No. 09/184,152, filed Nov. 2, 1998, now U.S. Pat. No. 5,969,134; which is a division of application Ser. No. 08/809,699, filed Mar. 27, 1997, now U.S. Pat. No. 5,932,730; which is a Section 371 Application of PCT/EP95/03903, filed Oct. 7, 1995, which claims the priority of German Application Numbers 19533023.4, filed Sep. 7, 1995 and P 44 36 851.8, filed Oct. 14, 1994.

The present invention relates to novel carboxylic acid derivatives, their preparation and use.

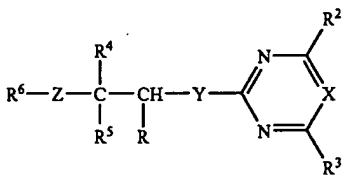
Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the following text, "endothelin" or "ET" signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this vasoconstriction is caused by binding of endothelin to its receptor (Nature, 332, (1988) 411–415; FEBS Letters, 231, (1988) 440–444 and Biochem. Biophys. Res. Commun., 154, (1988) 868–875).

Increased or abnormal release of endothelin causes persistent vasoconstruction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the literature that elevated plasma levels of endothelin were found in patients with hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, atherosclerosis and in the airways of asthmatics (Japan J. Hypertension, 12, (1989) 79, J. Vascular Med. Biology 2, (1990) 207, J. Am. Med. Association 264, (1990) 2868).

Accordingly, substances which specifically inhibit the binding of endothelin to the receptor ought also to antagonize the various abovementioned physiological effects of endothelin and therefore be valuable drugs.

We have found that certain carboxylic acid derivatives are good inhibitors of endothelin receptors.

The invention relates to carboxylic acid derivatives of the formula I



I

where R is formyl, tetrazole [sic], nitrile [sic], a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 hydrogen, hydroxyl, NH_2, $NH(C_1–C_4\text{-alkyl})$, $N(C_1–C_4\text{-alkyl})_2$, halogen, $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy or $C_1–C_4$-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, —NH or —NC_{1-4}-alkyl;

R^3 hydrogen, hydroxyl, NH_2, $NH(C_1–C_4\text{-Alkyl})$, $N(C_1–C_4\text{-alkyl})_2$, halogen, $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy, —NH—O—C_{1-4}-alkyl, $C_1–C_4$-alkylthio or CR^3 is linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy, phenoxy, $C_1–C_4$-alkylthio, amino, $C_1–C_4$-alkylamino or $C_1–C_4$-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2—, NH— or N-alkyl group, or $C_3–C_7$-cycloalkyl;

R^6 hydrogen, $C_1–C_8$-alkyl, $C_3–C_6$-alkenyl, $C_3–C_6$-alkynyl or $C_3–C_8$-cycloalkyl, where each of these radicals can be substituted one or more times by: halogen, nitro, cyano, $C_1–C_4$-alkoxy, $C_3–C_6$-alkenyloxy, $C_3–C_6$-alkynyloxy, $C_1–C_4$-alkylthio, $C_1–C_4$-haloalkoxy, $C_1–C_4$-alkylcarbonyl, $C_1–C_4$-alkoxycarbonyl, C_{3-8}-alkylcarbonylalkyl, $C_1–C_4$-alkylamino, di-$C_1–C_4$-alkylamino, phenyl or phenyl or phenoxy which is. substituted one or more times, eg. one to three times, by halogen, mitro, cyano, $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy or $C_1–C_4$-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy, phenoxy, $C_1–C_4$-alkylthio, $C_1–C_4$-alkylamino, $C_1–C_4$-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy, $C_1–C_4$-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: $C_1–C_4$-alkyl, $C_1–C_4$-haloalkyl, $C_1–C_4$-alkoxy, $C_1–C_4$-haloalkoxy and/or $C_1–C_4$-alkylthio;

with the proviso that R^6 can be hydrogen only when Z is not a single bond;

Y sulfur or oxygen or a single bond;

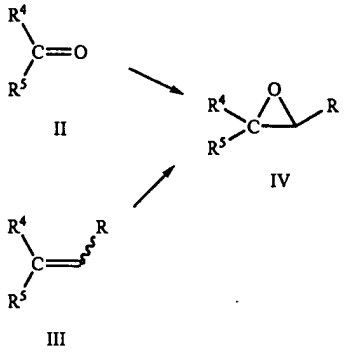
Z sulfur or oxygen or a single bond.

The compounds, and the intermediates for preparing them, such as IV and VI, may have one or more asymmetrical substituted carbon atoms. Such compounds may be in the form of the pure enantiomers or pure diastereomers or a mixture thereof. The use of an enantiomerically pure compound as active substance is preferred.

The invention furthermore relates to the use of the abovementioned carboxylic acid derivatives for producing drugs, in particular for producing endothelin receptor inhibitors.

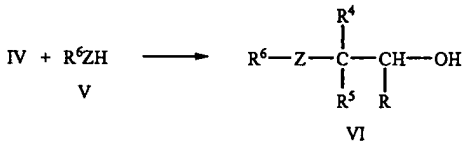
The invention furthermore relates to the preparation of the compounds of the formula IV in enantiomerically pure form. Enantio-selective epoxidation of an olefin with two phenyl substituents is known (J. Org. Chem. 59, 1994, 4378–4380). We have now found, surprisingly, that even ester groups in these systems permit epoxidation in high optical purity.

The preparation of the compounds according to the invention where Z is sulfur or oxygen starts from the epoxides IV, which are obtained in a conventional manner, eg. as described in J. March, Advanced Organic Chemistry, 2nd ed., 1983, page 862 and page 750, from the ketones II or the olefins III:



II IV III

Carboxylic acid derivatives of the general formula VI can be prepared by reacting the epoxides of the general formula IV (eg. with R=ROOR^{10} [sic]) with alcohols or thiols of the general formula V where R^6 and Z have the meanings stated in claim 1.



IV + R^{6}ZH → R^6—Z—C(R^4)(R^5)—CH(R)—OH

V VI

To do this, compounds of the general formula IV are heated with compounds of the formula V, in the molar ratio of about 1:1 to 1:7, preferably 1 to 3 mole equivalents, to 50–200 ° C., preferably 80–150° C.

The reaction can also take place in the presence of a diluent. All solvents which are inert toward the reagents used can be used for this purpose.

Examples of such solvents or diluents are water, aliphatic, alicyclic and aromatic hydrocarbons, which may in each case be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, alcohols, such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters such as ethyl acetate and amyl acetate, amides such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone, sulfoxides and sulfones, such as dimethyl sulfoxide and sulfolane, bases such as pyridine, cyclic ureas such as 1,3-dimethylimidazolidin-2-one and 1,3-dimethyl-3,4,5,6-tetra-hydro-2(1H)-pyrimidinone.

The reaction is preferably carried out at a temperature in the range from 0° C. to the boiling point of the solvent or mixture of solvents.

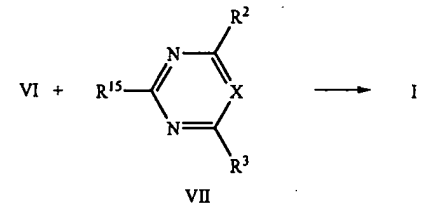
The presence of a catalyst may be advantageous. Suitable catalysts are strong organic and inorganic acids, and Lewis acids. Examples thereof are, inter alia, sulfuric acid, hydrochloric acid, trifluoroacetic acid, p-toluenesulfonic acid, boron trifluoride etherate and titanium(IV) alcoholates.

Compounds of the formula VI where R^4 and R^5 are cycloalkyl can also be prepared by subjecting compounds of the formula VI where R^4 and R^5 are phenyl, naphthyl, or phenyl or naphthyl substituted as described above, to a nuclear hydrogenation.

Compounds of the formula VI can be obtained in enantiomerically pure form by starting from enantiomerically pure compounds of the formula IV and reacting them in the manner described with compounds of the formula V.

It is furthermore possible to obtain enantiomerically pure compounds of the formula VI by carrying out a classical racemate resolution on racemic or diastereomeric compounds of the formula VI using suitable enantiomerically pure bases such as brucine, strychnine, quinine, quinidine, chinchonidine [sic], chinchonine [sic], yohimbine, morphine, dehydroabietylamine, ephedrine (–), (+), deoxyephedrine (+), (–) threo-2-amino-1-(p-nitrophenyl)-1,3-propanediol (+), (–) threo-2-(N,N-dimethylamino)-1-(p-nitrophenyl)-1,3-propanediol (+), (–) threo-2-amino-1-phenyl-1,3-propanediol (+), (–), α-methylbenzylamine (+), (–), α-(1-naphthyl)ethylamine (+), (–), α-(2-naphthyl)ethylamine (+), (–), aminomethylpinane, N,N-dimethyl-1-phenylethylamine, N-methyl-1-phenylethylamine, 4-nitrophenylethylamine, pseudoephedrine, norephedrine, norpseudoephedrine, amino acid derivatives, peptide derivatives.

The compounds according to the invention where Y is oxygen, and the remaining substituents have the meanings stated under the general formula I, can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula VI where the substituents have the stated meanings with compounds of the general formula VII



VI + VII → I

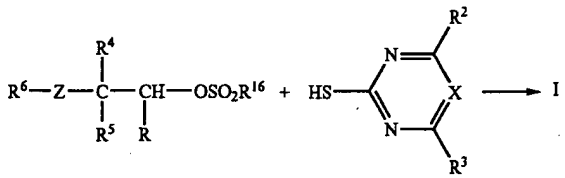
where R^{15} is halogen or R^{16}—SO$_2$—, where R^{16} can be C$_1$–C$_4$-alkyl, C$_1$–C$_4$-haloalkyl or phenyl. The reaction preferably takes place in one of the abovementioned inert diluents with the addition of a suitable base, ie. of a base which deprotonates the intermediate VI, in a temperature range from room temperature to the boiling point of the solvent.

Compounds of the formula VII are known, some of them can be bought, or they can be prepared in a generally known manner.

It is possible to use as base an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as an alkali metal carbonate, eg. sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an organometallic compound such as butyllithium, or an alkali metal amide such as lithium diisopropylamide.

The compounds according to the invention where Y is sulfur, and the remaining substituents have the meanings stated under the general formula I, can be prepared, for

example, by reacting carboxylic acid derivatives of the general formula VIII, which can be obtained in a known manner from compounds of the general formula VI and in which the substituents have the abovementioned meanings, with compounds of the general formula IX, where R^2, R^3 and X have the meanings stated under general formula I.

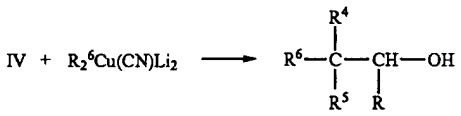


VIII IX

The reaction preferably takes place in one of the abovementioned inert diluents with the addition of a suitable base, ie. a base which deprotonates the intermediate IX, in a temperature range from room temperature to the boiling point of the solvent.

It is possible to use as base, besides those mentioned above, organic bases such as triethylamine, pyridine, imidazole or diazabicycloundecane [sic].

Carboxylic acid derivatives of the formula VIa (Z in formula VI=direct linkage) can be prepared by reacting epoxides of the formula IV with cuprates of the formula XI:



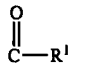
XI VIa

The cuprates can be prepared as described in Tetrahedron Letters 23, (1982) 3755.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, ie. compounds of the formula I where R is COOH, and initially converting these in a conventional manner into an activated form, such as a halide, an anhydride or imidazolide, and then reacting the latter with an appropriate hydroxy compound HOR^{10}. This reaction can be carried out in the usual solvents and often requires addition of a base, in which case those mentioned above are suitable. These two steps can also be simplified, for example, by allowing the carboxylic acid to act on the hydroxy compound in the presence of a dehydrating agent such as a carbodiimide.

In addition, it is also possible for compounds of the formula I to be prepared by starting from the salts of the corresponding carboxylic acids, ie. from compounds of the formula I where R is COR^1 and R^1 is OM, where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the formula R^1-A where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R^1-A with a reactive substituent A are known or can be easily obtained with general expert knowledge. This reaction can be carried out in conventional solvents and advantageously takes place with the addition of a base, in which case those mentioned above are suitable.

The radical R in formula I may vary widely. For example, R is a group



where R^1 has the following meanings:

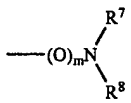
a) hydrogen;

b) succinylimidoxy [sic];

c) a five-membered heteroaromatic moiety linked by a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms, in particular fluorine and chlorine and/or one or two of the following radicals:

- C_1–C_4-alkyl such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl;
- C_1–C_4-haloalkyl, in particular C_1–C_2-haloalkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl;
- C_1–C_4-haloalkoxy, in particular C_1–C_2-haloalkoxy such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy and pentafluoroethoxy, in particular trifluoromethoxy;
- C_1–C_4-alkoxy such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy, 1-methylethoxy;
- C_1–C_4-alkylthio such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, 1,1-dimethylethylthio, in particular methylthio and ethylthio;

d) R^1 furthermore a radical



where m is 0 or 1 and R^7 and R^8, which can be identical or different, have the following meanings:

- hydrogen
- C_1–C_8-alkyl, in particular C_1–C_4-alkyl as mentioned above;
- C_3–C_6-alkenyl such as 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl,

2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl and 1-ethyl-2-methyl-2-propenyl, in particular 2-propenyl, 2-butenyl, 3-methyl-2-butenyl and 3-methyl-2-pentenyl;

C_3–C_6-alkynyl such as 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl., 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl and 1-ethyl-1-methyl-2-propynyl, preferably 2-propynyl, 2-butynyl, 1-methyl-2-propynyl and 1-methyl-2-butynyl, in particular 2-propynyl

C_3–C_8-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cyclooctyl, where these alkyl, cycloalkyl, alkenyl and alkynyl groups can each carry one to five halogen atoms, in particular fluorine or chlorine and/or one or two of the following groups:

C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-alkylthio, C_1–C_4-haloalkoxy as mentioned above, C_3–C_6-alkenyloxy, C_3–C_6-alkenylthio, C_3–C_6-alkynyloxy, C_3–C_6-alkynylthio, where the alkenyl and alkynyl constituents present in these radicals preferably have the abovementioned meanings;

C_1–C_4-alkylcarbonyl such as, in particular, methylcarbonyl, ethylcarbonyl, propylcarbonyl, 1-methylethylcarbonyl, butylcarbonyl, 1-methylpropylcarbonyl, 2-methylpropylcarbonyl, 1,1-dimethylethylcarbonyl;

C_1–C_4-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, 1-methylethoxycarbonyl, butyloxycarbonyl, 1-methylpropyloxycarbonyl, 2-methylpropyloxycarbonyl, 1,1-dimethylethoxycarbonyl;

C_3–C_6-alkenylcarbonyl, C_3–C_6-alkynylcarbonyl, C_3–C_6-alkenyloxycarbonyl and C_3–C_6-alkynyloxycarbonyl, where the alkenyl and alkynyl radicals are preferably defined as detailed above;

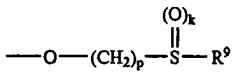
phenyl, unsubstituted or substituted one or more times, eg. one to three times, by halogen, nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy or C_1–C_4-alkylthio, such as 2-fluorophenyl, 3-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-nitrophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 4-trifluoroethoxyphenyl, 2-methylthiophenyl, 2,4-dichlorophenyl, 2-methoxy-3-methylphenyl, 2,4-dimethoxyphenyl, 2-nitro-5-cyanophenyl, 2,6-difluorophenyl;

di-C_1–C_4-alkylamino such as, in particular, dimethylamino, dipropylamino, N-propyl-N-methylamino, N-propyl-N-ethylamino, diisopropylamino, N-isopropyl-N-methylamino, N-isopropyl-N-ethylamino, N-isopropyl-N-propylamino;

R^7 and R^8 furthermore phenyl which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy or C_1–C_4-alkylthio, as mentioned above in particular;

or R^7 and R^8 together form a C_4–C_7-alkylene chain which is closed to form a ring, is unsubstituted or substituted, eg. substituted by C_1–C_4-alkyl, and may contain a heteroatom selected from the group consisting of oxygen, sulfur or nitrogen, such as —$(CH_2)_4$—, —$(CH_2)_5$—, —$(CH_2)_6$—, —$(CH_2)_7$—, —$(CH_2)_2$—O—$(CH_2)_2$—, —CH_2—S—$(CH_2)_3$—, —$(CH_2)_2$—O—$(CH_2)_3$—, —NH—$(CH_2)_3$—, —CH_2—NH—$(CH_2)_2$—, —CH_2—CH=CH—CH_2—, —CH=CH—$(CH_2)_3$—;

e) R^1 furthermore a group



where k is 0, 1 and 2, p is 1, 2, 3 and 4 and R^9 is C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_3–C_6-alkenyl, C_3–C_6-alkynyl or unsubstituted or substituted phenyl, as mentioned above in particular.

f) R^1 furthermore a radical OR^{10}, where R^{10} is:

hydrogen, the cation of an alkali metal such as lithium, sodium, potassium or the cation of an alkaline earth metal such as calcium, magnesium and barium or an environmentally compatible organic ammonium ion such as tertiary C_1–C_4-alkylammonium or the ammonium ion;

C_3–C_8-cycloalkyl as mentioned above, which may carry one to three C_1–C_4-alkyl groups;

C_1–C_8-alkyl such as, in particular, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl,

2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, which can carry one to five halogen atoms, in particular fluorine and chlorine and/or one of the following radicals:

C_1–C_4-alkoxy, C_1–C_4-alkylthio, cyano, C_1–C_4-alkylcarbonyl, C_3–C_8-cycloalkyl, C_1–C_4-alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, where the aromatic radicals in turn can carry in each case one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy and/or C_1–C_4-alkylthio, as mentioned above in particular;

a C_1–C_8-alkyl as mentioned above, which can carry one to five halogen atoms, in particular fluorine and/or chlorine, and carries one of the following radicals: a 5-membered heteroaromatic moiety containing one to three nitrogen atoms, or a 5-membered heteroaromatic moiety containing a nitrogen atom and an oxygen or sulfur atom, which can carry one to four halogen atoms and/or one or two of the following radicals:

nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, phenyl, C_1–C_4-haloalkoxy and/or C_1–C_4-alkylthio. Particular mention may be made of: 1-pyrazolyl,

3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3-isopropyl-5-isoxazolyl, 3-methyl-5-isoxazolyl, 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 3-ethyl-5-isoxazolyl, 3-phenyl-5-isoxazolyl, 3-tert-butyl-5-isoxazolyl;

a C_2–C_6-alkyl group which carries one of the following radicals in position 2: C_1–C_4-alkoxyimino, C_3–C_6-alkynyloxyimino, C_3–C_6-haloalkenyloxyimino or benzyloxyimino;

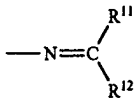
a C_3–C_6-alkenyl or C_3–C_6-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

R^{10} furthermore a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy,

C_1–C_4-haloalkoxy and/or C_1–C_4-alkylthio, as mentioned above in particular;

a 5-membered heteroaromatic moiety which is linked via a nitrogen atom, contains one to three nitrogen atoms and can carry one or two halogen atoms and/or one or two of the following radicals: C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, phenyl, C_1–C_4-haloalkoxy and/or C_1–C_4-alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;

R^{10} furthermore a group



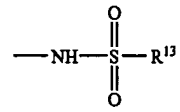
where R^{11} and R^{12}, which can be identical or different, are:

C_1–C_8-alkyl, C_3–C_6-alkenyl, C_3–C_6-alkynyl, C_3–C_8-cycloalkyl, it being possible for these radicals to carry a C_1–C_4-alkoxy, C_1–C_4-alkylthio and/or an unsubstituted or substituted phenyl radical, as mentioned above in particular;

phenyl which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy or C_1–C_4-alkylthio, where these radicals are, in particular, those mentioned above;

or R^{11} and R^{12} together form a C_3–C_{12}-alkylene chain which can carry one to three C_1–C_4-alkyl groups and contain a heteroatom from the group consisting of oxygen, sulfur and nitrogen, as mentioned in particular for R^7 and R^8.

g) R^1 furthermore a radical

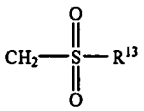


where R^{13} is:

C_1–C_4-alkyl, C_3–C_6-alkenyl, C_3–C_6-alkynyl, C_3–C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals to carry a C_1–C_4-alkoxy, C_1–C_4-alkylthio and/or a phenyl radical as mentioned above;

phenyl, unsubstituted or substituted, in particular as mentioned above.

h) R^1 a radical



where R^{13} has the abovementioned meaning.

R can furthermore be:

tetrazole [sic] or nitrile [sic].

In respect of the biological effect, preferred carboxylic acid derivatives of the general formula I, both as pure enantiomers and pure diastereomers or as mixture thereof, are those where the substituents have the following meanings:

R^2 hydrogen, hydroxyl, $N(C_1$–C_4-alkyl$)_2$, the C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio groups and halogen atoms mentioned in detail for R^1, especially chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy;

X nitrogen or CR^{14} where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- to 5-membered alkylene or alkenylene ring in which, in each case, a methylene group can be replaced by oxygen or sulfur, such as —CH_2—CH_2—O—, —CH=CH—O—, —CH_2—CH_2—CH_2—O—, —CH=CH—CH_2O—, in particular hydrogen, —CH_2—CH_2—O—, —$CH(CH_3)$—$CH(CH_3)$—O—, —$C(CH_3)$=$C(CH_3)$—O—, —CH=$C(CH_3)$—O— or —$C(CH_3)$=$C(CH_3)$—S;

R^3 the hydrogen, hydroxyl, $N(C_1$–C_4-alkyl$)_2$, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio groups and halogen atoms mentioned for R^1, especially chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl or naphthyl, which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio, C_1–C_4-alkylamino, di-C_1–C_4-alkylamino, C_1–C_4-alkylcarbonyl, C_1–C_4-alkoxycarbonyl; phenyl or naphthyl, which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group, or C_3–C_7-cycloalkyl;

R^6 C_1–C_8-alkyl, C_3–C_6-alkenyl, C_3–C_6-alkynyl or C_3–C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1–C_4-alkoxy, C_3–C_6-alkenyloxy, C_3–C_6-alkynyloxy, C_1–C_4-alkylthio, C_1–C_4-haloalkoxy, C_1–C_4-alkylcarbonyl, hydroxycarbonyl, C_1–C_4-alkoxycarbonyl, C_1–C_4-alkylamino, di-C_1–C_4-alkylamino or unsubstituted or substituted phenyl or phenoxy, as mentioned above in particular;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, phenoxy, C_1–C_4-alkylthio, C_1–C_4-akylamino [sic] or C_1–C_4-dialkylamino, as mentioned in particular for R^7 and R^4;

a five- or six-membered heteroaromatic moiety which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, C_1–C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy and/or C_1–C_4-alkylthio, as mentioned for R^4 in particular;

Y sulfur, oxygen or a single bond;

Z sulfur, oxygen, —SO—, —SO_2— or a single bond.

Particularly preferred compounds of the formula I, both as pure enantiomers and pure diastereomers or as mixture thereof, are those in which the substituents have the following meanings:

R^2 C_1–C_4-alkyl, C_1–C_4-alkoxy

X nitrogen or CR^{14}, where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- or 5-membered alkylene or alkenylene ring such as —CH_2—CH_2—CH_2—, —CH=CH—CH_2—, in which in each case a methylene group can be replaced by oxygen or sulfur, such as —CH_2—CH_2—O—, —CH=CH—O—, —CH_2—CH_2—CH_2—H—, —CH=CH—CH_2O—, in particular hydrogen, —CH_2—CH_2—O—, —$CH(CH_3)$—$CH(CH_3)$—O—, —$C(CH_3)$=$C(CH_3)$—O—, —CH=$C(CH_3)$—O— or —$C(CH_3)$=$C(CH_3)$—S;

R^3 the C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-alkylthio groups mentioned for R^1, or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl (identical or different) which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, hydroxyl, C_1–C_4-alkyl, C_1–C_4-alkoxy, C_1–C_4-alkylthio or

R^4 and R^5 are phenyl groups which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group; or

R^4 and R^5 are C_3–C_7-cycloalkyl;

R^6 C_1–C_8-alkyl, C_3–C_6-alkenyl or C_3–C_8-cycloalkyl, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1–C_4-alkoxy, C_3–C_6-alkenyloxy, C_1–C_4-alkylthio;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-haloalkoxy, phenoxy, C_1–C_4-alkylthio, C_1–C_4-akylamino [sic] or C_1–C_4-dialkylamino;

a five- or six-membered heteroaromatic moiety which contains a nitrogen atom and/or a sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy, C_1–C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1–C_4-alkyl, C_1–C_4-haloalkyl, C_1–C_4-alkoxy and/or C_1–C_4-alkyl-thio;

Y sulfur, oxygen or a single bond;

Z sulfur, oxygen, —SO—, —SO_2— or a single bond.

The compounds of the present invention provide a novel therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, or hypertension or kidney failure caused by ischemia or intoxication.

The good effect of the compounds can be shown in the following tests:

Receptor Binding Studies

Cloned human ET_A receptor-expressing CHO cells and guinea pig cerebellar membranes with >60% ET_B compared with ET_A receptors were used for binding studies.

The ET_A receptor-expressing CHO cells were grown in F_{12} medium containing 10% fetal calf serum, 1% glutamine, 100 U/ml penicillin and 0.2% streptomycin (Gibco BRL, Gaithersburg, Md., U.S.A.). After 48 h, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS for 5 min. Neutralization was then carried out with F_{12} medium, and the cells were collected by centrifugation at 300 ×g. To lyze the cells, the pellet was briefly washed with lysis buffer (5 mM Tris-HCl, pH 7.4 with 10% glycerol) and then incubated at a concentration of 10^7 cells/ml of lysis buffer at 4° C. for 30 min. The membranes were centrifuged at 20,000×g for 10 min, and the pellet was stored in liquid nitrogen;.

Guinea pig cerebella were homogenized in a Potter-Elvejhem homogenizer and [lacuna] obtained by differential centrifugation at 1000×g for 10 min and repeated centrifugation of the supernatant at 20,000×g for 10 min.

Binding Assays

For the ET_A and ET_B receptor binding assay, the membranes were suspended in incubation buffer (50 mM TrisHCl, pH 7.4 with 5 mM $MnCl_2$, 40 μg/ml bacitracin and 0.2% BSA) at a concentration of 50 μg of protein per assay mixture and incubated with 25 pM [125I]-ET_1 (ET_A receptor assay) or 25 pM [125I]-RZ_3 (ET_B receptor assay) in the presence and absence of test substance at 25° C. The nonspecific binding was determined using 10^{-7} M ET_1. After 30 min, the free and bound radioligand were separated by filtration through GF/B glass fiber filters (Whatman, England) on a Skatron cell collector (Skatron, Lier, Norway) and the filters were washed with ice-cold Tris-HCl buffer, pH 7.4 with 0.2% BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional in Vitro Assay System to Look for Endothelin Receptor (Subtype A) Antagonists

This assay system is a functional, cell-based assay for endothelin receptors. When certain cells are stimulated with endothelin 1 (ET1) they show an increase in the intracellular calcium concentration. This increase can be measured in intact cells loaded with calcium-sensitive dyes.

1-Fibroblasts which had been isolated from rats and in which an endogenous endothelin receptor of the A subtype had been detected were loaded with the fluorescent dye Fura 2-an as follows: after trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM $MgCl_{2,1}$ mM $CaCl_2$, 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of 2×10^6/ml and incubated with Fura 2-am (2 μM), Pluronics F-127 (0.04%) und DMSO (0.2%) at 37° C. in the dark for 30 min. The cells were then washed twice with buffer A and resuspended at 2×10^6/ml.

The fluorescence signal from 2×10^5 cells per ml with Ex/Em 380/510 was recorded continuously at 30° C. The test substances and, after an incubation time of 3 min, ET1 [lacuna] to the cells, the maximum change in the fluorescence was determined. The response of the cells to ET1 without previous addition of a test substance was used as control and was set equal to 100%.

Testing of ET Antagonists in Vivo

Male SD rats weighting 250–300 g were anesthetized with amobarbital, artifically ventilated, vagotomized and pithed. The carotid artery and jugular vein were cathetized [sic].

In control animals, intravenous administration of 1 μg/kg ET1 led to a distinct rise in blood pressure which persisted for a lengthy period.

The test animals received an i.v. injection of the test compounds (1 ml/kg) 5 min before the administration of ET1. To determine the ET-antagonistic properties, the rise in blood pressure in the test animals was compared with that in the control animals.

Endothelin-1-Induced Sudden Death in Mice

The principle of the test is the inhibition of the sudden heart death caused in mice by endothelin, which is probably induced by constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg endothelin in a volume of 5 ml/kg of body weight results in death of the animals within a few minutes.

The lethal endothelin-1 dose is checked in each case on a small group of animals. If the test substance is administered intravenously, the endothelin-1 injection which was lethal in the reference group usually takes place 5 min thereafter. With other modes of administration, the times before administration are extended, where appropriate up to several hours.

The survival rate is recorded, and effective doses which protect 50% of the animals (ED 50) from endothelin-induced heart death for 24 h or longer are determined.

Functional Test on Vessels for Endothelin Receptor Antagonists

Segments of rabbit aorta are, after an initial tension of 2 g and a relaxation time of 1 h in Krebs-Henseleit solution at 37° C. and pH 7.3–7.4, first induced to contract with K^+. After washing out, an endothelin dose-effect plot up to the maximum is constructed.

Potential endothelin antagonists are administered to other preparations of the same vessel 15 min before starting the endothelin dose-effect plot. The effects of the endothelin are calibrated as a % of the K^+-induced contraction. Effective endothelin antagonists result in a shift to the right in the endothelin dose-effect plot.

The compounds according to the invention can be administered orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperotoneally) in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal space.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. The daily dose of active substance is, as a rule, about 0.5–50 mg/kg of body weight on oral administration and about 0.1–10 mg/kg of body weight on parenteral administration.

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, eg. as uncoated or (film-) coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellent gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90% by weight of the active substance.

SYNTHESIS EXAMPLES

Example 1

Methyl
2-hydroxy-3-methoxy-3,3-diphenylpropionate

5 g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were dissolved in 50 ml of absolute methanol and, at 0° C., 0.1 ml of boron trifluoride etherate was added. The mixture was stirred at 0° C. for 2 h and at room temperature for a further 12 h. The solution vent was distilled out, the residue was taken up in ethyl acetate, washed with sodium bicarbonate solution and water and dried over magnesium sulfate. After removal of the solvent by distillation there remained 5.5 g (88%) of a pale yellow oil.

Example 2

Methyl
2-hydroxy-3-phenoxy-3,3-diphenylpropionate

5 g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate and 5.6 g (60 mmol) of phenol were heated together at 100° C. for 6 h. Removal of the excess phenol by distillation under high vacuum and purification of the residue by chromatography on silica gel with hexane/ethyl acetate mixtures resulted in 4.9 g (77%) of a pale yellow oil.

Example 3

Methyl 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate

2.86 g (10 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 40 ml of dimethylformamide, and 0.3 g (12 mmol) of sodium hydride was added. The mixture was stirred for 1 h and then 2.2 g (10 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine were added.

After stirring at room temperature for 24 h, cautious hydrolysis was carried out with 10 ml of water, the pH was adjusted to 5 with acetic acid, and the solvent was removed by distillation under high vacuum. The residue was taken up in 100 ml of ethyl acetate, washed with water and dried over magnesium sulfate, and the solvent was distilled out. The residue was mixed with 10 ml of ether, and the resulting precipitate was filtered off with suction. After drying, 3.48 g (82%) of a white powder remained.

Melting point 81° C.

Example 4

2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3, 3-diphenylpropionic acid

2.12 g (5 mmol) of methyl 2-(4,6-dimethoxy-pyrimidin-2-yl-oxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dioxane, 10 ml of 1 N KOH solution were added, and the mixture was stirred at 100° C. for 3 h. The solution was diluted with 300 ml of water and extracted with ethyl acetate to remove unreacted ester. The aqueous phase was then adjusted to pH 1–2 with dilute hydrochloric acid and extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent by distillation, the residue was mixed with an ether/hexane mixture, and the precipitate which formed was filtered off with suction. After drying, 1.85 g (90%) of a white powder remained.

Melting point 167° C.

Example 5

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3, 3-diphenyl Sodium [sic] Propionate

1.68 g (4 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionic acid are dissolved in 4 ml of 1N NaOH+100 ml of water. The solution is freeze-dried, and the sodium salt of the carboxylic acid used is obtained quantitatively.

10 g (34.9 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml each of methanol and glacial acetic acid, 1 ml of $RuO(OH)_2$ in dioxane was added, and hydrogenation was carried out with H_2 in an autoclave at 100° C. under 100 bar for 30 h. The catalyst was filtered off, the mixture was concentrated, mixed with ether and washed with NaCl solution, and the organic phase was dried and concentrated. 10, 1 g of methyl 3,3-dicyclohexyl-2-hydroxy-3-methoxypropionate were obtained as an oil.

Example 7

Methyl 2-[(4,6-dimethoxy-pyrimidin-2-yl)thio]-3-methoxy-3, 3-diphenylpropionate [sic]

7.16 g (25 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dichloromethane, 3 g (30 mmol) of triethylamine were added, and 3.2 g (28 mmol) of methanesulfonyl chloride were added dropwise while stirring. The mixture was stirred at room temperature for 2 h, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in DMF and added dropwise at 0° C. to a suspension of 12.9 g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4 g (100 mmol) of sodium bicarbonate in 100 ml of DMF. After stirring at room temperature for 2 h and at 60° C. for a further 2 h, the mixture was poured into 1 liter of ice-water, and the resulting precipitate was filtered off with suction. After drying, 3.19 g (29%) of a white powder remained.

Example 8

Methyl 2-hydroxy-3,3-diphenylbutyrate

1.5 g (5.9 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate dissolved in 10 ml of absolute ether were added dropwise to a cuprate solution which had been prepared from 635 mg (7 mmol) of copper(I) cyanide dissolved in 10 ml of absolute ether and 8.14 ml (13 mmol) of a 1.6 normal methyllithium solution and had been cooled to −78° C. The solution was stirred at −78° C. for 1 h and then allowed to warm to room temperature. It was subsequently diluted with 100 ml of ether and 100 ml of water, and the ether phase was washed with dilute citric acid and with sodium bicarbonate solution and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate mixtures to result in 250 mg (16%) of a pale yellow oil.

Example 9

2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid

91.11 g (0.5 mol) of benzophenone and 45.92 g (0.85 mol) of sodium methoxide were suspended in 150 ml of methyl tert-butyl ether (MTB) at room temperature. After cooling to −10° C., 92.24 g (0.85 mol) of methyl chloroacetate were added in such a way that the internal temperature rose to 40° C. while continuing to cool in a bath at −10° C. The mixture was then stirred without cooling at the autogenous temperature for one hour. After addition of 250 ml of water and brief stirring, the aqueous phase was separated off. The MTB phase was washed with 250 ml of dilute sodium chloride solution. After the solvent had been changed to methanol (250 ml), a solution of 1 g of p-toluenesulfonic acid in 10 ml of methanol was added at room temperature. The mixture was stirred at autogenous temperature for one hour and then heated to reflux. While distilling out the methanol, 400 g of a 10% strength sodium hydroxide solution was added dropwise, and finally 60 ml of water were added. The methanol was distilled out until the bottom temperature reached 97° C. After cooling to 55° C., 190 ml of MTB were added and the mixture was acidified to pH 2 with about 77 ml of concentrated HCl. After cooling to room temperature, the aqueous phase was separated off and the organic phase was concentrated by distilling out 60 ml of MtB [sic]. The product was crystallized by adding 500 ml of heptane and slowly cooling to room temperature. The coarsely crystalline solid was filtered off with suction, washed with heptane and dried to constant weight in a vacuum oven at 40° C.

Yield: 108.9 g (80%), HPLC>99.5% area.

Example 10

S-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid (Racemate Resolution with L-proline Methyl Ester)

148.8 g of a 30% strength methanolic sodium methanolate solution (0.826 mol) were added dropwise to 240 g of a 57%

strength methanolic L-proline methyl ester hydrochloride solution (0.826 mol) at room temperature, and 2.4 l of MTB and 225 g (0.826 mol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid were added. After 2680 ml of MTB/methanol mixture had been distilled out with simultaneous dropwise addition of 2.4 l of MTB, the mixture was slowly cooled to room temperature, the crystals (R-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid×L-proline methyl ester) were filtered off with suction, and the solid was washed with 150 ml of MTB. The filtrate was concentrated by distilling out 1.5 l of MTB, and 1.0 l of water was added. The pH was adjusted to 1.2 with concentrated hydrochloric acid at room temperature and, after stirring and phase separation, the aqueous phase was separated off and extracted with 0.4 l of MTB. The combined organic phases were extracted with 0.4 l of water. The residue after the MTB had been stripped off was dissolved in 650 ml of toluene under reflux, and the product was crystallized by seeding and slow cooling. Filtration with suction, washing with toluene and drying in a vacuum oven resulted in 78.7 g of S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (yield 35% based on the racemate).

Chiral HPLC: 100% pure HPLC: 99.8%

Example 11

S-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid (Racemate Resolution with (S)-1-(4-nitrophenyl)ethylamine)

30.5 g (0.184 mol) of (S)-1-(4-nitrophenyl)ethylamine were added to 100 g (0.368 mol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid in 750 ml of acetone and 750 ml of MTB under reflux, the mixture was seeded, boiled under reflux for one hour and slowly cooled to room temperature for crystallization. The crystals (S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid x (S)-1-(4-ni-trophenyl)ethylamine) were filtered off with suction and washed with MTB. The residue was suspended in 500 ml of water and 350 ml of MTB and then the pH was adjusted to 1.2 with concentrated hydrochloric acid at room temperature, and, after stirring and phase separation, the aqueous phase was separated off and extracted with 150 ml of MTB. The combined organic phases were extracted with 100 ml of water. 370 ml of MTB were distilled out and then 390 ml of n-heptane were added under reflux, and the mixture was slowly cooled to room temperature while the product crystallized. Filtration with suction, washing with n-heptane and drying in a vacuum oven resulted in 35.0 g of S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (yield 35% based on the racemate).

Chiral HPLC: 100% pure HPLC: 99.8%

Example 12

Benzyl 3-methoxy-2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3,3-diphenylpropionate

24.48 g (90 mmol) of 3-methoxy-3,3-diphenyl-2-hydroxypropionic acid were dissolved in 150 ml of DMF, and 13.7 g (99 mmol) of potassium carbonate were added. The suspension was stirred at room temperature for 30 min. Then 10.7 ml (90 mmol) of benzyl bromide were added dropwise over the course of 5 min, and the mixture was stirred for 1 h, during which the temperature rose to 32° C.

To this mixture were successively added 24.84 g (180 mmol) of K_2CO_3 and 20.52 g (90 mmol) of 2-methanesulfonyl-4-methoxy-6,7-dihydro-5H-cyclopentapyridine [sic], and the mixture was stirred at 80° C. for 3 h.

For workup, the contents of the flask were diluted with about 600 ml of H_2O and cautiously acidified with concentrated HCl, and 250 ml of ethyl acetate were added. 31.4 g of pure product precipitated and were filtered off.

The ethyl acetate phase was separated from the mother liquor, the aqueous phase was extracted again with ethyl acetate, and the combined organic phases were concentrated. The oily residue (19 g) was purified by chromatography (cyclohexane/ethyl acetate=9/1) to result in a further 10.5 g of pure product.

Total yield: 41.9 g (82.2 mmol)≙91% Melting point 143–147° C. MS: MH^+=511

Example 13

3-Methoxy-2-(4-methoxy-(6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3,3-diphenylpropionic [sic] Acid

40 g (78.4 mmol) of benzyl 3-methoxy-2-(4-methoxy-6,7-di-hydro-5H-cyclopentapyrimidin-2-yloxy)-3,3-diphenylpropionate were dissolved in 400 ml of ethyl acetate/methanol (4:1), about 500 mg of palladium on active carbon (10%) were added, and the mixture was exposed to a hydrogen atmosphere until no further gas was taken up. The catalyst was filtered off, the solution was evaporated, and the residue was crystallized from ether.

Example 14

Ethyl 2S-3,3-diphenyloxirane-2-carboxylate

2.57 g (10.2 mmol) of ethyl 3,3-diphenylacrylate and 464 mg of 4-phenylpyridine N-oxide were dissolved in 24 ml of methylene chloride, and 432 mg (6.5 mol %) of (5,5)-(+)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomaganese(III) chloride were added. While cooling in ice, 6.4 ml of a 12% strength sodium hypochloride [sic] solution were added, and the mixture was stirred while cooling in ice for 30 min and at room temperature overnight. The solution was diluted to 200 ml with water, extracted with ether, dried and evaporated. 2.85 g of a colorless oil were obtained. Purification by NPLC [sic] (cyclo-hexane: ethyl acetate=9:1) resulted in 1.12 g of oil with an enantiomer ratio of about 8:1 in favor of the S configuration.

^{1}H-NMR [$CDCl_3$], δ=1.0 (t, 3H); 3.9 (m, 3H); 7.3 (m, 10H)

Example 15

2-Methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidin-4-ol [sic]

46.9 g (330 mmol) of methyl cyclopentanone-2-carboxylate and 53.5 g (192 mmol) of 5-methylisothiourea [sic] sulfate were successively added to 29.6 g (528 mmol) of KOH in 396 ml of methanol, and the mixture was stirred at room temperature overnight, acidified with 1N hydrochloric acid and diluted with water. The crystals which separated out were filtered off with suction and dried. 20 g of crystals were obtained.

Example 16

Sulfanyl 4–Chloro-2-methyl-6,7-dihydro-5H-cyclopentapyrimidine [sic]

255 ml of phosphorus oxychloride were added to 20 g (110 mmol) [lacuna], and the mixture was stirred at 80° C. for 3 hours. Phosphorus oxychloride was evaporated off, ice was added to the residue, and the crystals which separated out were filtered off with suction. 18.5 g of a brownish solid were obtained.

Example 17

4-Methoxy-2-methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidine [sic]

18.05 g (90 mmol) of 4-chloro-2-methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidine [sic] were dissolved in 200 ml of methanol. At 45° C., 16.7 g of sodium methoxide (as 30% strength solutions [sic] in methanol) were added dropwise, and the mixture was stirred for 2 hours. The solution was evaporated, taken up in ethyl acetate and acidified with dilute hydrochloric acid, and the ethyl acetate extract was evaporated. 15.5 g of an oil remained.

^{1}H-NMR [DMSO], δ=2.1 (quintet, 2H); 2.5 (s, 3H); 2.8 (dt, 4H); 3.9 (s, 3H) ppm

Example 18

2-Methylsulfonyl-4-methoxy-6,7-dihydro-5H-cyclopentopyrimidine [sic]

15 g (76.2 mmol) of 4-methoxy-2-methylsulfonyl-6,7-dihydro-5H-cyclopentapyrimidine [sic] were dissolved in 160 ml of glacial acetic acid/methylene chloride (1:1), and 1.3 g of sodium tungstate were added. At 35° C., 17.5 ml (170 ml [sic]) of a 30% strength H_2O_2solution were added dropwise. The mixture was then diluted with 500 ml of water and 100 ml of methylene chloride, and the organic phase was separated off, dried and evaporated. 14 g of oil remained and were crystallized from ether.

^{1}H-NMR [$CDCl_3$], δ=2.2 (quintet, 2H); 3.0 (dt., 4H); 3.3 (s, 3H); 4.1 (s, 3H) ppm

Example 19

1-Benzenesulfonyl-3-(4,6-dimethoxy-2-pyrimidinyloxy)-4-methoxy-4,4-diphenyl-2-butanone

0.37 g (2.4 mmol) of phenyl methane [sic] sulfone were dissolved in 10 ml of dry THF and then, at −70° C., 2 eq. of butyllithium (2.94 ml; 1.6 molar solution in hexane) were added dropwise. After 1 h at −70° C., 1 g (2.4 mmol) of methyl 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropynoate [sic] dissolved in 5 ml of THF was added dropwise. The reaction mixture was then stirred at −70° C. for 1 h and at −10° C. for 1 h and then warmed to room temperature.

For workup, about 10 ml of saturated NH_4Cl solution were added dropwise, thorough extraction with ethyl acetate was carried out, and the combined organic phases [lacuna] with-saturated N—Cl [sic] solution and dried over Na_2SO_4. The residue obtained after drying and concentration was purified by chromatography on silica gel (n-heptane/ethyl acetate 15%→30%) and subsequently MPLC on RP silica gel (acetonitrile/H_2O+TFA); 0.3 g of a white amorphous powder was obtained as product.

Example 20

3,3-Diphenyloxiram-2-carbonitrile [sic]

3.1 g (54.9 mmol) of sodium methoxide were suspended in 20 ml of dry THF and then, at −10° C., a mixture of 5 g (27.4 mmol) of benzophenone and 4.2 g (54.9 mmol) of chloroacetonitrile was added dropwise.

The reaction mixture was stirred at −10° C. for about 2 h, then poured into water and extracted several times with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography on silica gel (n-heptane/ethyl acetate).

Yield: 1.2 g (20%) ^{1}H-NMR [$CDCl_3$], δ=3.9 (s, 1H); 7.4–7.5 (m, 10 H) ppm

Example 21

2-Hydroxy-3-methoxy-3,3-diphenylpropionitrile

6.5 [lacuna] (29.4 mmol) of 3,3-diphenyloxirane-2-carbonitrile were dissolved in 60 ml of methanol and, at 0° C., about 2 ml of boron trifluoride etherate solution were added. The mixture was stirred further at 0° C. for 1 h and then at room temperature overnight. For workup it was diluted with diethyl ether and washed with saturated NaCl solution, and the organic phase was dried over Na_2SO_4 and concentrated. The residue comprised 7.3 g of a white amorphous powder which was used directly in the subsequent reactions.

^{1}H-NMR [$CDCl_3$], δ=2.95 (broad s, OH), 3.15 (s, 3H), 5.3 (s, 1H), 7.3–7.5 (m, 10) ppm

Example 22

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionitrile

7.3 g (28.8 mmol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionitrile were dissolved in 90 ml of DMF, and 4 g (28.8 mmol) of K_2CO_3 and 6.3 g (28 mmol) of 2-methanesulfonyl-4,6-dimethoxypyrimidine were added. The mixture was stirred at room temperature for about 12 h, then poured into water and extracted with ethyl acetate. The combined organic phases were washed again with H_2O, dried and concentrated. The residue obtained in this way was then purified by chromatography on silica gel (n-hepane/ethyl acetate).

Yield: 6.9 g of white amorphous powder FAB-MS: 392 ($M+H^+$) ^{1}H-NMR [$CDCl_3$], δ=3.3 (s, 3H); 4.95 (s, 6H), 5.85 (s, 1H); 6.3 (s, 1H); 7.3–7.5 (m, 10H) ppm

Example 23

5-[2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenyl)propyl]-1H-tetrazole [sic]

0.5 g (1.3 mmol) of nitrile was dissolved in 10 ml of toluene, and 85 mg (1.3 mmol) of NaN_3 and 460 mg (1.4 mmol) of Bu_3SnCl were successively added, and then the mixture was refluxed for about 40 h. Cooling was followed by dilution with ethyl acetate and washing with 10% aqueous KF solution and with NaCl solution. After drying over

$MgSo_4$ and concentration there remained 1.0 g of a yellow oil, which was purified by chromatography on silica gel (n-heptane/ethyl acetate).

Concentration of the fractions resulted in 60 mg of the 1H-tetra-zole and 110 mg of the 1-methyltetrazole, each as amorphous white solids.

5-[2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenyl)propyl]-1H-tetrazole [sic]

Electrospray-MS: 435 ($M+H^+$) ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.28 (s, 3H), 3.85 (s, 6H), 5.75 (s, 1H), 7.25–7.40 (m, 10H), 7.50 (s, 1H).

5-[2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenyl)propyl]-1-methyltetrazole [sic]

Electrospray-MS; 471 ($M+H^+$) ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.0 (s, 3H), 3.35 (s, 3H9 [sic], 3.80 (s, 6H), 5.75 (s, 1H), 7.30–7.40 (m, 11H).

Example 24

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methylsulfinyl-3,3-diphenylpropionic Acid

1.2 g (2.9 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methylsulfonyl-3,3-diphenylpropionic [sic] acid were introduced into 15 ml of glacial acetic acid at 0° C. and 294 µl of 30% strength H_2O_2 were added dropwise. The mixture was stirred at room temperature overnight, poured into water, extracted with CH_2Cl_2 and washed with sodium thiosulfate solution and brine. After drying, 1 g of substance was isolated as a white foam.

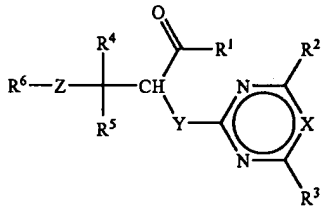
Example 25

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methylsulfonyl-3,3-diphenylpropionic Acid

0.6 g (1.45 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methylsulfonyl-3,3-diphenylpropionic [sic] acid was introduced into 15 ml of glacial acetic acid at room temperature, and 294 µl of 30% strength H_2O_2 were added dropwise. The mixture was stirred at room temperature overnight, heated at 50° C. for a further 3 h, poured into water and washed with sodium thiosulfate solution and brine. After drying, 400 mg were isolated as a white solid.

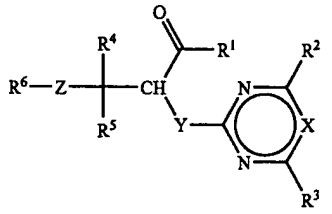
The compounds listed in Table 1 [sic] can be prepared in a similar way.

TABLE I



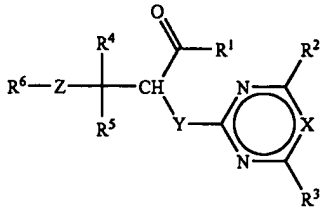
No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m. p. [° C.]
I-195	OMe	Phenyl	Methyl	OMe	OMe	CH	O	O	81
I-196	OH	Phenyl	Methyl	OMe	OMe	CH	O	O	167
I-197	OH	Phenyl	CH_2—CH_2—S—CH_3	OMe	OMe	CH	O	O	
I-198	OH	Phenyl	Ethyl	OMe	OMe	CH	O	O	81 (decomp.)
I-199	OH	Phenyl	iso-Propyl	OMe	OMe	CH	O	O	182
I-200	OH	Phenyl	Methyl	OMe	OMe	CH	O	S	168
I-201	OH	Phenyl	CH_2—CH_2—SO_2—$CH(CH_3)_2$	OMe	OMe	CH	O	O	
I-202	OH	Phenyl	CH_2—CH_2—SO_2—$CH(CH_3)_2$	OMe	OMe	CH	S	O	
I-203	OH	Phenyl	CH_2—CH_2—SO_2—$CH(CH_3)_2$	OMe	OMe	C—$CH(CH_3)_2$	O	O	
I-204	OH	Phenyl	CH_2—CH_2—SO_2—$CH(CH_3)_2$	OMe	OMe	C—$CH(CH_3)_3$	O	O	
I-205	OH	Phenyl	CH_2—CH_2—SO_2—$CH(CH_3)_2$	OMe	NH-OCH_3	CH	O	O	
I-206	OH	Phenyl	n-Propyl	OMe	OMe	CH	O	O	174
I-207	OMe	Phenyl	n-Propyl	OMe	OMe	CH	O	O	
I-208	OH	Phenyl	n-Prnpyl	OEt	OEt	CH	O	O	
I-209	OH	Phenyl	n-Butyl	OMe	OMe	CH	O	O	
I-210	OH	Phenyl	iso-Butyl	OMe	OMe	CH	O	O	
I-211	OH	Phenyl	iso-Butyl	OMe	O—CH_2—CH_2—C		O	O	
I-212	OH	Phenyl	tert.-Butyl	OMe	OMe	CH	O	O	
I-213	OH	Phenyl	Cyclopropyl	OMe	OMe	CH	O	O	
I-214	OH	Phenyl	Cyclopentyl	OMe	OMe	CH	O	O	
I-215	OH	Phenyl	Cyclohexyl	OMe	OMe	CH	O	O	
I-216	OH	Phenyl	$(CH_3)_3C$—CH_2—CH_2	OEt	OEt	CH	O	O	
I-217	OH	Phenyl	$(CH_3)_2CH$—CH_2—CH_2—CH_2	OMe	OMe	CH	O	O	173
I-218	OH	Phenyl	HO—CH_2—CH_2	OMe	OMe	CH	O	O	
I-219	OH	Phenyl	HO_2C—$(CH_2)_2$—	OMe	OMe	CH	O	O	
I-220	OH	Phenyl	Cyclopropylmethylene [sic]	OMe	OMe	CH	O	O	115
I-221	OH	Phenyl	H	OMe	OMe	CH	O	O	

TABLE I-continued



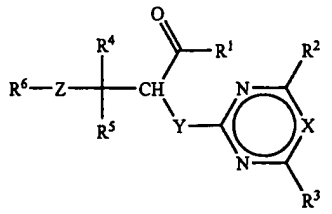
No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m. p. [° C.]
I-222	OH	Phenyl	Methyl	OMe	OMe	CH	O	—	
I-223	OH	Phenyl	Phenyl	OMe	OMe	CH	O	O	136
I-224	OH	Phenyl	Phenyl	OMe	O—CH(CH_3)—CH_2—C		O	O	
I-225	OMe	Phenyl	Phenyl	OMe	OMe	CH	O	O	
I-226	OH	Phenyl	4-Isopropyl-Phenyl	OMe	OMe	CH	O	O	
I-227	OH	Phenyl	4-Me-S-Phenyl	OMe	OMe	CH	O	O	
I-228	OH	Phenyl	4-Me-O-Phenyl	OMe	OMe	CH	O	O	
I-229	OH	Phenyl	3-Et-Phenyl	OMe	OMe	CH	O	O	
I-230	OH	Phenyl	2-Me-Phenyl	OMe	OMe	CH	O	O	
I-231	OH	Phenyl	2-Cl—Phenyl	OMe	OMe	CH	O	O	
I-232	OH	Phenyl	3-Br—Phenyl	OMe	OMe	CH	O	O	
I-233	OH	Phenyl	4-F—Phenyl	OMe	OMe	CH	O	O	
I-234	OH	Phenyl	4-F—Phenyl	OMe	OMe	CH	S	O	
I-235	OH	Phenyl	4-CH_3-Phenyl	OMe	OMe	CH	O	O	
I-236	OH	Phenyl	3-NO_2-Phenyl	OMe	OMe	CH	O	O	
I-237	OH	Phenyl	2-HO-Phenyl	OMe	OMe	CH	O	O	
I-238	OH	Phenyl	3,4-Dimethoxyphenyl	OMe	OMe	CH	O	O	
I-239	OH	Phenyl	3,4-Dioxomethylenephenyl [sic]	OMe	OMe	CH	O	O	
I-240	OH	Phenyl	3,4,5-Trimethoxyphenyl	OMe	OMe	CH	O	O	
I-241	OH	Phenyl	Benzyl	OMe	OMe	CH	O	O	
I-242	OH	Phenyl	2-Cl-Benzyl	OMe	OMe	CH	O	O	
I-243	OH	Phenyl	3-Br-Benzyl	OMe	OMe	CH	O	O	
I-244	OH	Phenyl	4-F-Benzyl	OMe	OMe	CH	O	O	
I-245	OH	Phenyl	2-Me-Benzyl	OMe	OMe	CH	O	O	
I-246	OH	Phenyl	2-Me-Benzyl	OMe	O—CH=CH—C		O	O	
I-247	OH	Phenyl	3-Et-Benzyl	OMe	OMe	CH	O	O	
I-248	OH	Phenyl	4-iso-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-249	OH	Phenyl	4-NO_2-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-250	OH	Phenyl	2-Me-5-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-251	OH	Phenyl	2-Me-5-Propyl-Benzyl	OEt	OEt	CH	O	O	
I-252	OH	Phenyl	4-Me-2-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-253	OH	Phenyl	3,4-Dioxomethylenebenzyl [sic]	OMe	OMe	CH	O	O	
I-254	OH	4-F-Phenyl	Methyl	OMe	OMe	CH	O	O	163–165 (decomp.)
I-255	OMe	4-F-Phenyl	Methyl	OEt	OEt	CH	O	O	
I-256	OH	4-Cl-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-257	OH	4-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-258	OH	4-Me-O-Phenyl	Ethyl	OMe	OMe	CH	O	O	
I-259	OH	4-Me-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-260	OH	4-Me-Phenyl	Methyl	OMe	O—CH_2—CH_2—C		O	O	
I-261	OH	3-CF_3-Phenyl	n-Propyl	OMe	OMe	CH	O	O	
I-262	OH	3-CF_3-Phenyl	n-Propyl	OMe	O—CH(CH_3)—CH_2—C		O	O	
I-263	OH	4-NO_2-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-264	OH	4-NO_2-Phenyl	Methyl	OMe	O—CH=CH—C		O	O	
I-265	OH	3-Cl-Phenyl	Ethyl	OMe	OMe	CH	O	O	
I-266	OH	2-F-Phenyl	Methyl	OMe	OMe	CH	O	O	193–194 (decomp.)
I-267	OH	2-F-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-268	OH	2-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-269	OH	2-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-270	OH	3,4-Dimethoxyphenyl	Methyl	OMe	OMe	CH	O	O	
I-271	OH	3,4-Dioxomethylenephenyl [sic]	Methyl	OMe	OMe	CH	O	O	
I-272	OH	p-CF_3-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-273	OH	Phenyl	Methyl	OMe	OEt	CH	O	O	
I-274	OMe	Phenyl	Methyl	OMe	OEt	CH	S	O	
I-275	OH	Phenyl	Ethyl	OMe	NH-OMe	CH	O	O	
I-276	OH	p-Me-O-Phenyl	n-Propyl	OMe	OCF_3	CH	O	O	
I-277	OH	Phenyl	Methyl	OMe	CF_3	CH	O	O	
I-278	OH	Phenyl	Methyl	OMe	CF_3	N	O	O	
I-279	OH	3,4-Dimethoxyphenyl	Benzyl	Me	Me		O	O	

TABLE I-continued



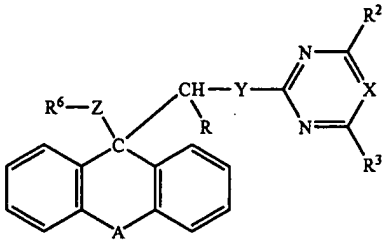
No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m. p. [° C.]
I-280	OH	3,4-Dimethoxyphenyl	Methyl	OMe		O—CH_2—CH_2—C	O	O	
I-281	OH	Phenyl	Methyl	OMe		O—CH_2—CH_2—C	O	O	126 (decomp.)
I-282	OH	Phenyl	Methyl	OMe		O—$CH(CH_3)$—CH_2—C	O	O	
I-283	OH	Phenyl	Methyl	OMe		$N(CH_3)$—CH=CH—C	O	O	118
I-284	OH	Phenyl	Methyl	OMe		S—$C(CH_3)$=$C(CH_3)$—C	O	O	
I-285	OH	Phenyl	Methyl	OMe		O—$C(CH_3)$=CH=C	O	O	
I-286	OH	Phenyl	Methyl	Me		O—$C(CH_3)$=CH—C	O	O	
I-287	OH	Phenyl	Methyl	Me		O—CH=CH—C	O	O	
I-288	OH	4-F-phenyl	Methyl	Me		S—CH=CH—C	O	O	
I-289	OH	4-F-phenyl	H	OMe	OMe	CH	O	O	
I-290	OH	Phenyl	Methyl	OMe		CH_2—CH_2—CH_2—C	O	O	149–151 (decomp.)
I-291	OH	Phenyl	Methyl	Methyl		CH_2—CH_2—CH_2—C	O	O	157 (decomp.)
I-292	OH	Phenyl	Methyl	Ethyl		CH_2—CH_2—CH_2—CH_2—C	O	O	
I-293	OH	Phenyl	Methyl	OMe		CH_2—CH_2—CH_2—CH_2—C	O	O	
I-294	OH	Phenyl	Methyl	Me	Me	CH	O	O	
I-295	OH	Phenyl	Methyl	Et	Et	CH	O	O	
I-296	OH	Phenyl	Methyl	Me	Me	C—CH_3	O	O	
I-297	OH	Phenyl	Methyl	OMe	Me	CH	O	O	
I-298	OH	Cyclohexyl	Methyl	OMe	OMe	CH	O	O	
I-299	OH	Cyclohexyl	Methyl	OMe		CH_2—CH_2—CH_2—C	O	O	
I-300	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S	
I-301	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	S	134
I-302	OCH_3	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S	
I-303	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-304	OCH_3	2-Fluorophenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-305	OC_2H_5	3-Chlorophenyl	Methyl	OCH_3	OCH_3	N	O	O	
I-306	$ON(CH_3)_2$	4-Bromophenyl	Methyl	CF_3	CF_3	CH	S	O	
I-307	O—CH_2—C=CH	Phenyl	Ethyl	OCH_3	CF_3	CH	O	O	
I-308	OH	Phenyl	Propyl	OCH_3	OCF_3	CH	O	S	
I-309	OCH_3	Phenyl	i-Propyl	OCH_3	CH_3	CH	O	O	
I-310	OC_2H_5	Phenyl	s-Butyl	OCH_3	Cl	CH	S	O	
I-311	$ON(CH_3)_2$	2-Methylphenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-312	$ON(CH_3)_2$	3-Methoxyphenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-313	ON=$C(CH_3)_2$	4-Nitrophenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-314	$ON(CH_3)_2$	Phenyl	1-Phenylpropyn-3-yl	OCH_3	OCF_3	N	O	S	
I-315	ON=$C(CH_3)_2$	2-Hydroxyphenyl	Methyl	OCH_3	CH_3	N	O	O	
I-316	$ONSO_2C_6H_5$	3-Trifluoromethylphenyl	Methyl	OCH_3	Cl	N	O	O	
I-317	NHPhenyl	4-Dimethylaminophenyl	Methyl	OCH_3	OCH_3	CH	S	O	
I-318	OC_2H_5	Phenyl	Trifluoroethyl	CH_3	CH_3	CH	O	O	
I-319	$ON(CH_3)_2$	Phenyl	Benzyl	Cl	Cl	CH	O	O	
I-320	$ON(CH_3)_2$	Phenyl	2-Methoxyethyl	OCH_3		—O—CH_2—CH_2—	S	O	
I-321	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-322	OH	Phenyl	Phenyl	OCH_3		—O—CH_2—CH_2—	O	O	
I-323	OH	Phenyl	Phenyl	OCH_3	OCH_3	N	O	O	
I-324	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	O	
I-325	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	S	
I-326	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-327	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-328	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-329	OH	—$(CH_2)_5$—	Phenyl	Phenyl	OCH_3	CH	O	O	
I-330	OH	Phenyl	2-Thiazolyl	OCH_3	OCH_3	CH	O	O	
I-331	OCH_3	2-Fluorophenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-332	OC_2H_5	3-Chlorophenyl	Phenyl	OCH_3	OCH_3	N	O	O	
I-333	$ON(CH_3)_2$	4-Bromophenyl	Phenyl	CF_3	CF_3	CH	O	O	
I-334	O—CH_2≡CH	Phenyl	2-Fluorophenyl	OCH_3	CF_3	CH	O	O	
I-335	OH	Phenyl	3-Chlorophenyl	OCH_3	OCF_3	CH	O	S	
I-336	OCH_3	Phenyl	4-Bromophenyl	OCH_3	CH_3	CH	O	O	
I-337	OC_2H_5	Phenyl	4-Thiazolyl	OCH_3	Cl	CH	S	O	
I-338	$ON(CH_3)_2$	2-Methylphenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-339	ON=$C(CH_3)_2$	3-Methoxyphenyl	Phenyl	OCH_3	OCH_3	CH	O	O	

TABLE I-continued



No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m. p. [° C.]
I-340	OH	Phenyl	Methyl	OCH_3	—CH_2—CH_2—CH_2—C		O	O	
I-341	OH	4-Fluorophenyl	Methyl	OCH_3	OCH_3	CH	O	O	168 (decomp.)
I-342	OH	4-Fluorophenyl	Methyl	OCH_3	—CH_2—CH_2—CH_2—C		O	O	
I-343	NH—SO—C_6H_5	4-Nitrophenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-344	OCH_3	Phenyl	3-Imidazolyl	OCH_3	—O—CH_2—CH_2		O	O	
I-345	OC_2H_5	Phenyl	4-Imidazolyl	OCH_3	CF_3	N	S	O	
I-346	$ON(CH_3)_2$	Phenyl	2-Pyrazolyl	OCH_3	OCF_3	N	O	S	
I-347	ON=$C(CH_3)_2$	2-Hydroxyphenyl Phenyl	OCH_3	CH_3	N	O	O		
I-348	NH—SO_2—C_6H_5	3-Trifluoromethylphenyl	Phenyl	OCH_3	Cl	N	O	O	
I-349	NHPhenyl	4-Dimethylaminophenyl	Phenyl	OCH_3	OCH_3	CH	S	O	
I-350	ONa	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	S	
I-351	O—CH_2—C≡C	Phenyl	Phenyl	OCH_3	OCH_3	N	S	S	
I-352	OH	Phenyl	Phenyl	CF_3	CF_3	CH	O	S	
I-353	OCH_3	Phenyl	Phenyl	OCF_3	OCF_3	CH	O	O	
I-354	OC_2H_5	Phenyl	2-Dimethylaminophenyl	CH_3	CH_3	CH	O	O	
I-355	$ON(CH_3)_2$	Phenyl	3-Hydroxyphenyl	Cl	Cl	CH	O	O	
I-356	ON=$C(CH_3)_2$	Phenyl	4-Trifluoromethylphenyl	OCH_3	—O—CH_2—CH_2—		S	O	
I-357	NH—SO_2—C_6H_5	Phenyl	2-Oxazolyl	OCH_3	CF_3	N	S	S	
I-358	OH	Phenyl	Methyl	CH_3	CH_3	CH	O	O	
I-359	OH	Cyclohexyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-360	OH	Cyclohexyl	Methyl	OCH_3	CH_2—CH_2—CH—C		O	O	
I-361	OH	Phenyl	Methyl	$N(CH_3)_2$	$N(CH_3)_2$	CH	O	O	
I-362	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	SO_2	
I-363	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	SO_2	
I-364	OH	3-F-Phenyl	Me	OMe	OMe	CH	O	O	
I-365	OH	3-F-Phenyl	Me	OMe	CH_2—CH_2—CH_2—C		O	O	
I-366	OH	4-F-Phenyl	Me	OMe	CH_2—CH_2—CH_2—C		O	O	142–143 191° C.
I-367	OH	3-MeO-Phenyl	Me	OMe	CH_2—CH_2—CH_2—C		O	O	158–161 (decomp.)
I-368	OH	3-MeO-Phenyl	Me	OMe	OMe	CH	O	O	
I-369	OH	3-MeO-Phenyl	Et	OMe	CH_2—CH_2—CH_2—C		O	O	
I-370	OH	Phenyl	HO-CH_2—CH_2	OMe	CH_2—CH_2—CH_2—C		O	O	
I-371	OH	Phenyl	Me	NMe_2	NMe_2	N	O	O	181
I-372	OH	Phenyl	Me	OMe	OMe	N	O	O	
I-373	OH								
I-374	NH—SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-375	NH—SO_2-Me	Phenyl	Me	OMe	OMe	CH	O	O	
I-376	CH_2—SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-377	CH_2—SO_2-Me	Phenyl	Me	OMe	OMe	CH	O	O	
I-378	—CN	Phenyl	Me	OMe	OMe	CH	O	O	
I-379	Tetrazole [sic]	Phenyl	Me	OMe	OMe	CH	O	O	
I-380	NH—SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	167
I-381	N-Methyltetrazole [sic]	Phenyl	Me	OMe	Me	CH	O	O	
I-382	ONa	Phenyl	Me	OMe	—O—CH_2—CH_2—C—		O	O	122–139 (zers.)
I-383	OH	o-F-Phenyl	Me	OMe	—O—CH_2—CH_2—C—		O	O	140–144 (decomp.)
I-384	OH	m-Me-Phenyl	Me	OMe	OMe	CH	O	O	169–177
I-385	OH	m-Me-Phenyl	Me	OMe	—O—CH_2—CH_2—C—		O	O	119–135 (decomp.)
I-386	OH	p-F-Phenyl	Me	OMe	Me	CH	O	O	137–140 (decomp.)
I-387	OH	m-F-Phenyl	Me	Me	—O—CH_2—CH_2—C—		O	O	150–152
I-388	OH	p-F-Phenyl	Me	Me	—O—CH_2—CH_2—C—		O	O	169–170

TABLE II



No.	R^1	A	R^6	R^2	R^3	X	Y	Z	m. p. [° C.]
II-1	OH	Bond	Methyl	OMe	OMe	CH	O	O	96–98
II-2	OH	CH_2	Methyl	OMe	OMe	CH	O	O	
II-3	OH	CH_2—CH_2	Methyl	OMe	OMe	CH	O	O	
II-4	OH	CH═CH	Methyl	OMe	OMe	CH	O	O	
II-5	OH	O	Methyl	OMe	OMe	CH	O	O	
II-6	OH	S	Methyl	OMe	OMe	CH	O	O	
II-7	OH	$NH(CH_3)$	Methyl	OMe	OMe	CH	O	O	
II-8	OH	Bond	Isopropyl	OMe	OMe	CH	O	O	137–139
II-9	OH	Bond	p-Isopropylphenyl	OMe	OMe	CH	O	O	
II-10	OH	Bond	Benzyl	OMe	OMe	CH	O	O	
II-11	OH	CH═CH	Ethyl	OMe	OMe	CH	O	O	
II-12	OH	CH═CH	$(CH_3)_2$—CH_2—CH_2	OMe	OMe	CH	O	O	
II-13	OH	CH═CH	Cyclopropylmethylene [sic]	OMe	OMe	CH	O	O	
II-14	OH	CH═CH	Methyl	OMe	O—CH_2—CH_2—C		O	O	
II-15	OH	CH_2—CH_2	Ethyl	OMe	O—CH═CH—C		O	O	
II-16	OH	CH_2═CH_2	Methyl	OMe	CH_2—CH_2—CH_2—C		O	O	
II-17	OH	Bond	Methyl	OMe	CH_2—CH_2—CH_2—C		O	O	147

Example 35

Receptor binding data were measured by the binding assay described above for the compounds listed below.

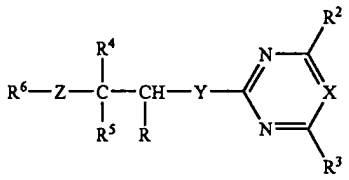
The results are shown in Table 2 [sic].

TABLE 2[sic]

	Receptor binding data (K_i values)	
Compound	ET_A [nM]	ET_B [nM]
I-2	6	34
I-29	86	180
I-5	12	160
I-4	7	2500
I-87	1	57
I.89	86	9300
I-103	0.4	29
I-107	3	485
I-12	19	1700
I-26	23	2000
I-23	209	1100
I-47	150	1500
I-60	33	970
I-96	0.6	56
II-3	107	7300
II-1	28	2300

We claim:

1. A compound having the formula:



wherein:

X is CH;

Y is oxygen;

Z is oxygen;

R is CO_2H;

R^2 is methyl;

R^3 is methyl;

R^4 is phenyl;

R^5 is phenyl; and

R^6 is methyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein said compound is an optically active enantiomer.

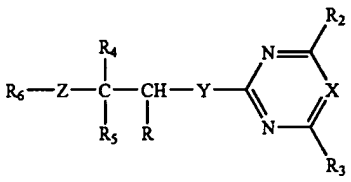
3. The compound of claim 2, wherein the enantiomer is the S enantiomer.

4. The compound of claim 3, wherein the enantiomer is the pure form of the S enantiomer.

5. The compound of claim 2, wherein the enantiomer is the R enantiomer.

6. The compound of claim 5, wherein the enantiomer is the pure form of the R enantiomer.

7. A pharmaceutical composition comprising a compound having the formula:



wherein:

X is CH;

Y is oxygen;

Z is oxygen;

R is CO_2H;

R^2 is methyl;

R^3 is methyl;

R^4 is phenyl;

R^5 is phenyl;

R^6 is methyl; or a

pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

8. The composition of claim **7**, wherein said composition is suitable for oral, parenteral, or nasopharyngeal delivery.

9. The composition of claim **7**, wherein the composition is in a solid form.

10. The composition of claim **7**, wherein the composition is in a liquid form.

11. The composition of claim **7**, wherein the composition is in the form of a tablet, capsule, powder, granule, suppository, solution, colloid, ointment, cream, vapor or spray.

12. The composition of claim **7**, wherein the carrier comprises a tablet binder, filler, preservative, tablet disintegrant, flow regulator, plasticizer, wetting agent, dispersant, emulsifier, solvent, release-slowing agent, antioxidant, or propellant gas.

13. The composition of claim **7**, wherein the compound is an optically active enantiomer.

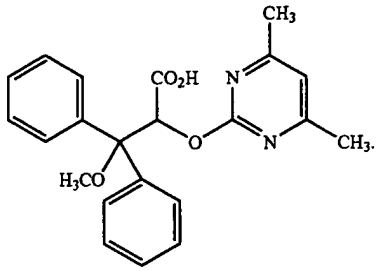
14. The composition of claim **13**, wherein the enantiomer is the S enantiomer.

15. The composition of claim **14**, wherein the enantiomer is the pure form of the S enantiomer.

16. The composition of claim **13**, wherein the enantiomer is the R enantiomer.

17. The composition of claim **16**, wherein the enantiomer is the pure form of the R enantiomer.

18. The compound



* * * * *

EXHIBIT
G

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT		Docket No.: ABB10010P0114US
Applicant(s):	Reichers et al.	Confirmation No.:
Serial No.:	10/602,275	Filing Date: June 24, 2003
Group Art Unit:	1624	Examiner: Bruck Kifle
Invention:	Novel Carboxylic Acid Derivatives, Their Preparation And Use	

The owner*, Abbott GmbH & Co. KG, of 100% (one hundred percent) interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term **prior patent** No. 5,932,730 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2, if appropriate.

1. ☐ For submission on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.*

☒ Terminal Disclaimer fee under 37 CFR 1.20(d) is enclosed in the amount of: ☒ $130.00 (large entity)
☐ $ 65.00 (small entity)

☐ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account Number 23-0785. A duplicate copy of this sheet is enclosed.

8/24/05
Date

Martin L. Katz, Reg. No. 25,011

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500 West Madison Street
Chicago, Illinois 60661-2511
312/876-1800

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner) Form PTO/SB/96 may be used for making this certification. See MPEP §324.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket No.: ABB10010P0114US

Applicant(s):	Reichers et al.	Confirmation No.:	
Serial No.:	10/602,275	Filing Date:	June 24, 2003
Group Art Unit:	1624	Examiner:	Bruck Kifle
Invention:	Novel Carboxylic Acid Derivatives, Their Preparation And Use		

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket No.: ABB10010P0114US

Applicant(s):	Reichers et al.	Confirmation No.:	
Serial No.:	10/602,275	Filing Date:	June 24, 2003
Group Art Unit:	1624	Examiner:	Bruck Kifle
Invention:	Novel Carboxylic Acid Derivatives, Their Preparation And Use		

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is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2, if appropriate.

1. ☐ For submission on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.*

☒ Terminal Disclaimer fee under 37 CFR 1.20(d) is enclosed in the amount of: ☒ $130.00 (large entity)
☐ $ 65.00 (small entity)

☐ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account Number 23-0785. A duplicate copy of this sheet is enclosed.

8/24/05
Date

Martin L. Katz, Reg. No. 25,019

WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
Citigroup Center, Suite 3800
500 West Madison Street
Chicago, Illinois 60661-2511
312/876-1800

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner) Form PTO/SB/96 may be used for making this certification. See MPEP §324.

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United States Patent and Trademark Office

Maintenance Fees Window Dates

07/30/2007 10:42 AM EDT

Patent Number: 7109205

Application Number: 10602275

	4th Year	8th Year	12th Year
Open Date	09/21/2009	09/19/2013	09/19/2017
Surcharge Date	03/22/2010	03/20/2014	03/20/2018
Close Date	09/20/2010	09/19/2014	09/19/2018

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United States Patent and Trademark Office

Patent Maintenance Fees		07/30/2007 10:43 AM EDT	
Patent Number:	7109205	**Application Number:**	10602275
Issue Date:	09/19/2006	**Filing Date:**	06/24/2003
Window Opens:	09/21/2009	**Surcharge Date:**	03/22/2010
Window Closes:	09/20/2010	**Payment Year:**	
Entity Status:	LARGE		
Customer Number:	000000		
Street Address:	WOOD, PHILLIPS, KATZ, CLARK & MORTIMER		
City:	CHICAGO		
State:	IL		
Zip Code:	60661		
Phone Number:	(312) 876-1800		
Currently there are no fees due.			

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EXHIBIT
H

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

June 3, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Subject: **Investigational New Drug Application BSF 208075 for Pulmonary Arterial Hypertension** **Serial No. 000 (Initial Submission)**

Dear Sir or Madam:

On behalf of Myogen, Inc., Quintiles, Inc. is submitting with this correspondence an initial Investigational New Drug Application (IND) for a new chemical entity, BSF 208075, an ET_A selective endothelin receptor antagonist, being investigated in patients with pulmonary arterial hypertension. In accordance with 21 CFR Part 312 this thirty volume IND is submitted in triplicate.

To aid in the evaluation of the application, Section 10 of this IND contains additional information regarding communication with the Division of Cardio-Renal Drug Products that took place previously under IND 63,412. This includes a summary of the actions taken by Myogen in response to the Division's recommendations and copies of correspondence and meeting minutes that discussed the investigation of BSF 208075 for the indication of pulmonary arterial hypertension. In addition, Section 11 of this IND contains a copy of the informed consent form for protocol AMB-220, which is submitted in Section 6.

Also, please find enclosed for submission a letter from Myogen, Inc. transferring the responsibility as US Agent and Authorized Representative to Quintiles, Inc.; a letter from Quintiles accepting the transfer of responsibility; and an official Transfer of US Regulatory Obligations form delineating the duties being transferred.

Any questions concerning this Investigational New Drug Application should be directed to:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

Sincerely,

Cynthia Kirk, Ph.D., RAC
Executive Director
Regulatory and Technical Services
Quintiles, Inc. Kansas City

Innovative therapies targeting heart muscle disease

Myogen

June 3, 2002

Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research (HFD-110)
Food and Drug Administration

Subject: **BSF 208075**
Selective Endothelin Receptor Antagonist
For Pulmonary Arterial Hypertension

General Correspondence:
Transfer of responsibility as US Agent and Authorized Representative

Dear Dr. Throckmorton:

Effective June 3, 2002, Myogen, Inc. is authorizing Quintiles, Inc., Kansas City, MO to act as its U.S. Agent and Authorized Representative for BSF 208075, an ETA Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Myogen, Inc., 7577 West 103rd Ave. #212, Westminster, CO 80021-5426, telephone (303) 464-5221.

Sincerely,

J. William Freytag
President, CEO and Chairman
Myogen, Inc.

7575 W. 103rd Ave suite #102 • Westminster, CO 80021-5426• Phone: 303-410-6666 • Fax: 303-410-6667

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

June 3, 2002

Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research (HFD-110)
Food and Drug Administration

Subject: **BSF 208075**
Selective Endothelin Receptor Antagonist
For Pulmonary Arterial Hypertension

General Correspondence:
Acceptance of responsibility as US Agent and Authorized Representative

Dear Dr. Throckmorton:

Effective June 3, 2002, Quintiles, Inc., Kansas City, MO assumes the responsibility from Myogen, Inc. as the U.S. Agent and Authorized Representative for BSF 208075, an ET_A Selective Endothelin Receptor Antagonist, being investigated in patients with pulmonary arterial hypertension. The duties to be performed by Quintiles, Inc. are:

- Submission of the IND
- Verbal and written interaction with the FDA
- Conduct of meetings with the FDA
- Submission of the IND annual reports
- Submission of IND amendments
- General IND maintenance

The contact person at Quintiles, Inc., is:

Marguerite Enlow, Pharm.D., RAC
Associate Regulatory Director,
Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708
Telephone: (816) 767-6408
Fax: (816) 767-7373

If you have any questions regarding the above information, please do not hesitate to contact me at Quintiles, Inc., P.O. Box 9708, Kansas City, Missouri 64134-0708, telephone (816) 767-6493.

Sincerely,

Cynthia Kirk, Ph.D., RAC
Executive Director
Regulatory and Technical Services
Quintiles, Inc. Kansas City

TRANSFER OF US FDA REGULATORY OBLIGATIONS FOR INVESTIGATIONAL PHARMACEUTICAL AND BIOLOGIC PRODUCTS UNDER AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION (21 CFR 312.52)

Sponsor:	Myogen	Project Code/ Work Order Number:	Not Assigned
Product Name:	BSF 208075	IND Number:	Not Available
Indication:	Pulmonary Arterial Hypertension	Protocol Number:	All protocols

	Responsibility	21 CFR Reference	Obligation Assigned to: Sponsor	Quintiles
A.	1. Preparation of all or part of an IND application	312.23	X	X
	2. Submission of IND application to FDA		☐	X
B.	Maintain an IND with the following amendments, as necessary:			
	1. Preparation of Protocol amendments (includes new protocols, changes in protocols, adding new investigators)	312.30	X	☐
	2. Preparation of Chemistry, Manufacturing, and Control amendments	312.31	X	☐
	3. Preparation of Pharmacology and Toxicology amendments	312.31	X	☐
	4. Preparation of Clinical amendments	312.31	X	☐
	5. Safety Reports	312.32		
	(a) Preparation of initial report		X	☐
	(b) Preparation of follow-up reports		X	☐
	(c) Notifications to FDA (phone/fax or written)		☐	X
	(d) Notifications to investigators		X	☐
	6. Preparation of Annual Reports	312.33	X	X
	7. Preparation of response to request for information or clinical hold	312.41, 42	X	X
	8. Preparation of letter to withdraw an IND	312.38	X	X
	9. **Act as IND agent; submit all amendments to FDA**	312.23 -.42	☐	X
C.	Selecting investigators and monitors	312.53		
	1. Select qualified investigators[1]	312.53 (a)	X	☐
	2. Control of drug[1]			
	(a) Approve drug shipment after review of required information from investigator (including signed Form FDA 1572, CV)	312.53 (c)	X	☐
	(b) Ship drug to approved investigators	312.53 (b)	☐	X
	3. Provide qualified monitors[1]	312.53 (d)	X	☐

4. Informing investigators[1]			
(a) Review with investigators their regulatory responsibilities	312.60 -.69	X	☐
(b) Supply investigator's brochure	312.55 (a)	X	☐
(c) Inform investigators of new safety information about the study drug	312.55 (b)	X	☐
D. Review of ongoing investigations	312.56		
1. Monitoring the investigation (includes ensuring that investigator is complying with all commitments in Section 9 of the signed Form FDA-1572)[1]	312.56(a)	X	☐
2. Discontinue investigator participation if not compliant[1] Note: If the sponsor does not discontinue an investigator who Quintiles believes to be significantly non-compliant, Quintiles will request a complete transfer of regulatory obligation for that site back to the sponsor.	312.56(b)	X	☐
3. Initial evaluation of all adverse events[1]	312.56 (c)	X	☐
4. Upon discontinuation of a study[1]:	312.56 (d)		
(a) Notify FDA		☐	X
(b) Notify IRBs and investigators		X	☐
(b) Assure disposition of drug from sites to sponsor		X	☐
E. Recordkeeping and record retention	312.57		
1. Maintain sponsor records and reports for 2 years after study end or marketing application approved, for	312.57(a)(b)		
(a) Records of drug shipment and disposition		X	☐
(b) All correspondence with sponsor, FDA, IRB, investigators		X	☐
(c) Records concerning adverse effects		X	☐
(d) Other records required by FDA		X	☐
2. Retain reserve samples of test articles and reference standards used in bioequivalence or bioavailability studies	312.57 (c)	X	☐
F. Disposition of unused supply of investigational drug	312.59		
1. Assure return of drug from site to sponsor[1]		X	☐
2. Conduct final disposition or destruction of drug[1]		X	☐
G. If requested by FDA, submission of sponsor's records and reports to FDA for inspection	312.58 (a)	X	X
H. Apply for FDA approval to export investigational drug if:	312.110	☐	☐
(a) Drug is not approved for marketing in any country, AND			
(b) Drug is not under an active IND, AND			
(c) Drug is not being exported to one of listed countries[2]			
X Not applicable			
I. Represent sponsor in resolution of disputes with FDA	312.48	X	X
J. Obtain investigator financial disclosure information	[FR 2/2/98]	X	☐

[1] If responsibility for an item is shared between the sponsor and Quintiles, both boxes will be checked. Quintiles' responsibility for the item is limited to the list of sites attached to this document. **This must be confirmed in the contract.**

[2] Listed countries: Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and current member nations of the European Union and European Economic Area.

According to 21 CFR 312.52(b), "A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations." The assignment of responsibility does not preclude either the sponsor or the CRO from participating in the requirements of the CFR.

The sponsor hereby transfers to Quintiles, Inc. the responsibilities indicated above under the column titled "Obligation Assigned to QUINTILES," effective Jan 15 2002 (date).

Sponsor: MYOGEN	QUINTILES
[signature]	Marguerite Enlow, M.D.
Signature	Regulatory & Technical Services Signature
J. William Freytag	Marguerite Enlow
Printed Name	Printed Name
President, CEO and Chairman	Associate Director
Title	Title
1-15-02	1/15/02
Date	Date

EXHIBIT
I

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,915

Myogen, Inc.
Attention: Mr. J. William Freytag
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021

Dear Mr. Freytag:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 64,915

Sponsor: Myogen, Inc.

Name of Drug: BSF 208075

Date of Submission: June 3, 2002

Date of Receipt: June 4, 2002

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before July 3, 2002, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information.[21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5333.

Sincerely yours,

Zelda McDonald
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Quintiles, Inc.
Cynthia Kirk, Ph.D., RAC
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
6/10/02 02:21:20 PM

EXHIBIT
J

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Colorado, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
7575 West 103rd Ave., #102
Westmister, CO 80021-5426

Dear Ms. Tanner:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Letairis (ambrisentan) 5 and 10 mg Tablets

Date of Application: December 13, 2006

Date of Receipt: December 18, 2006

Our Reference Number: NDA 22-081

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2007 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fromm
1/10/2007 02:31:37 PM

EXHIBIT
K

REGULATORY REVIEW PERIOD ACTIVITIES

The table below summarizes representative formal submissions and contacts between the drug sponsor and FDA throughout the regulatory review period. The table is not comprehensive as to every event corresponding to a given type of submission, nor does it reflect regular email and telephone contacts throughout the regulatory review period to discuss upcoming submissions and provide preliminary information. Following the table below is a more comprehensive list of regulatory review activities.

2002-06-03	**Initial submission date of IND No. 64,915**
2002-06-04	**Receipt date of IND No. 64,915**
2002-06-28	Revised informed consent form
2002-07-17	Updated information for drug substance and drug product
2002-08-30	Clinical protocol amendment
2002-10-29	Response to request for information – CMC
2002-11-06	Information amendment: clinical
2002-12-09	Response to request for information: 26 wk. animal toxicity studies
2003-01-02	Rationale & study summary for additional long-term protocol
2003-01-13	Response to request for additional information regarding IND
2003-01-14	Response to request re safety monitoring plans for clinical trial
2003-02-07	Protocol amendment: new protocol
2003-03-05	IND 15-Day ADR Report
2003-03-11	Investigator notification of IND safety report for elevated liver function tests
2003-04-01	Duration of chronic toxicity study
2003-05-02	IND safety report: follow-up
2003-05-15	Type B meeting request
2003-05-15	Fax requesting End of Phase II meeting
2003-08-05	Information package for 27 August 2003 meeting
2003-08-27	End of Phase II meeting with FDA
2003-10-08	New Phase III protocols
2003-12-02	Change in clinical protocol
2003-12-18	Request for special protocol assessment 2-year mouse carcinogenicity protocol
2004-02-13	Information amendment
2004-03-17	Pharmacology-toxicology 2-Year rat and mouse final protocols

2004-03-25	Type C meeting request
2004-05-06	Protocol amendments
2004-05-27	Orphan drug application: amendment
2004-08-09	Type C meeting request to discuss proposed changes to the ambrisentan program
2004-08-27	Initial written report: 15-day safety alert report
2004-09-27	Type C meeting information package
2004-10-13	Meeting
2004-12-07	Information amendment: pharmacology/toxicology: 2-year rat and mouse carcinogenicity
2005-02-15	New protocol
2005-03-09	Information amendment: pharmacology/toxicology: 2-year rat and mouse carcinogenicity studies
2005-04-05	Response to request for information
2005-04-12	Protocol amendment
2005-05-24	Converting ARIES-2 study sites to ARIES-1
2005-08-04	Information amendment: Chemistry, Manufacturing and Controls
2005-08-22	Data analysis plan for FDA feedback
2005-08-22	Fax re 7 day safety report - initial manufacturer's report
2005-08-25	IND safety reports
2005-09-07	Request for FDA review of QT/QTc study proposal
2005-09-12	Type C meeting request: development plan for biopharmaceutics and clinical pharmacology
2005-10-04	Information amendment: Chemistry, Manufacturing, and Controls
2005-10-04	IND safety report: follow-up to a written report
2005-10-13	Meeting re PK and clinical pharmacology
2005-10-18	New protocol and new investigator
2005-10-19	Teleconference re data analysis plans
2005-11-04	New protocol and new investigator
2005-11-07	Response to FDA comments on QT/QTc study design
2005-11-11	Protocol amendment: change in protocol
2005-11-11	Information amendment: pharmacology/toxicology 2-year rat and mouse carcinogenicity studies
2005-11-29	Data analysis plans
2005-11-29	Information amendment: pharmacology/toxicology
2005-11-30	Data analysis plan for population pharmacokinetic modeling
2005-11-30	Protocol: new protocol and new investigator
2005-11-30	Data analysis plans

2005-12-15	Teleconference re PK/PD development plans
2005-12-19	IND safety report: initial written report
2005-12-19	Protocol amendment: new protocol and new investigators
2006-01-09	IND safety report: follow-up to a written report
2006-01-13	Protocol amendment: change in protocol
2006-01-16	IND safety report: follow-up to a written report
2006-01-23	Protocol amendment: change in protocol
2006-01-27	IND safety report: follow-up to a written report
2006-02-09	Request for fast track designation
2006-02-21	Response to IND correspondence
2006-03-02	IND safety report: follow-up to a written report
2006-03-08	Type B meeting request: Pre-NDA
2006-03-15	Requirements and format of NDA
2006-03-23	Information amendment: pharmacology/toxicology
2006-04-19	Information amendment: pharmacology/toxicology
2006-04-21	Pre-NDA briefing document
2006-04-27	IND safety report: initial written report
2006-05-04	Information amendment: pharmacology/toxicology
2006-05-08	Response to FDA comments
2006-05-17	Type B meeting request: pre-NDA CMC
2006-05-19	Pre-NDA meeting
2006-05-26	IND safety report: follow-up to a written report
2006-06-02	IND safety report: initial written report
2006-06-14	Request feedback on non-clinical NDA format and content
2006-06-15	Information amendment: clinical CSR's
2006-06-28	CMC pre-NDA information package
2006-07-06	IND safety report: initial and follow-up written safety report
2006-07-26	Pre-NDA CMC meeting
2006-10-06	CMC- proposed commercial dissolution method
2006-10-13	Proposal for 4-month safety update
2006-10-30	IND safety report: follow-up to a written report
2006-11-07	IND safety report: follow-up to a written report
2006-11-28	IND safety report: follow-up to a written report
2006-12-07	Transfer of sponsorship
2006-12-13	**Submission of NDA No. 22-081**
2006-12-18	**Receipt of NDA No. 22-081**
2007-01-09	Teleconference

2007-01-18	Response to letter re submission of complete CRF's and filing process
2007-01-19	Telephone call regarding inspections at clinical sites that conducted Phase 3 studies
2007-01-22	Email regarding revised protocol document-presence of sponsors
2007-02-09	Teleconference re protocols for capturing lab values
2007-02-13	Response to questions on the distribution of ambrisentan and RiskMAP
2007-02-15	IND safety report: follow-up to a written report
2007-03-03	Request for meeting to discuss status of review of NDA 22-081. Update on Amendments submitted to NDA
2007-03-07	Unformatted prescribing information; option to resolve formatting
2007-03-20	FDA site inspection
2007-03-20	Response regarding request for efficacy & safety datasets
2007-03-21	IND safety report: initial written report
2007-03-22	Protocol amendment: change to protocol
2007-03-29	90-day teleconference
2007-04-03	Request for Meeting to discuss dosing interval
2007-04-10	Protocol amendment: new protocol and new investigator
2007-04-16	Response to questions regarding dissolution profiles
2007-04-19	Population pharmacokinetic (PK) data analysis plan (DAP) amendment
2007-04-19	Response to questions regarding bioanalytical assay issues
2007-04-23	Response regarding randomization
2007-04-24	Protocol amendment: change to protocol
2007-04-30	IND safety report: follow up to a written safety report
2007-05-02	Protocol amendment. New protocol and new investigator
2007-05-04	DDMAC promotional materials. Request for perspective review and advisory comments for product launch materials
2007-05-08	Protocol amendment: change to protocol
2007-05-25	IND safety report: follow up to a written safety report
2007-05-25	Meeting
2007-05-31	Proposed pediatric study request
2007-05-31	IND safety report: follow-up to a written report
2007-06-07	Protocol amendment: new investigators
2007-06-07	IND safety report: follow-up to a written report
2007-06-15	**Marketing approval letter for NDA 22-081**

Back to Main TOC

Ambrisentan: Pulmonary Arterial Hypertension - IND 64,915

Product	Department	Country	Document Date	Book Number	Document Type	Document Title	E-Copy	Keywords
1	Regulatory	US	7/20/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-199	S-199	64,915
1	Regulatory	US	7/10/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-198	S-198	64,915
1	Regulatory	US	6/28/2007	Temp 113	FDA Submission - IND	Annual Report. S-197	S-197	64,915
1	Regulatory	US	6/22/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-196	S-196	64,915
1	Regulatory	US	6/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-195	S-195	64,915
1	Regulatory	US	6/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-194	S-194	64,915
1	Regulatory	US	6/7/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-193	S-193	64,915
1	Regulatory	US	6/7/2007	Temp 110	FDA Submission - IND	Protocol Amendment. New Investigators. S-192	S-192	64,915
1	Regulatory	US	5/31/2007	Temp 110	FDA Submission - IND	IND Safety Report . Follow-up to a Written Report. S-191	S-191	64,915
1	Regulatory	US	5/31/2007	Temp 110	FDA Submission - IND	Other. Proposed Pediatric Study Request. S-190	S-190	64,915
1	Regulatory	US	5/29/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-189	S-189	64,915
1	Regulatory	US	5/25/2007	Temp 110	FDA Submission - IND	IND Safety Report. Follow-up to a Written Report. S-188	S-188	64,915
1	Regulatory	US	5/18/2007	Temp 110	FDA Correspondence - Letter (Fax)	L.Tanner/N.Stockbridge - The 7 Day Safety Report	2007-05-18_64915_CORR_LETTER_FAX_LTANNER_NSTOCKBRIDGE.pdf	64,915
1	Regulatory	US	5/18/2007	Temp 110	FDA Correspondence - Email	L.Tanner/D.Brum - Email with the 7-day Safety Report Documents attachment.	2007-05-18_64915_CORR_EMAIL_DBRUM_LTANNER.pdf	64,915
1	Regulatory	US	5/18/2007	Temp 110	FDA Submission - IND	IND Safety Report. Initial Written Report. S-187	S-187	64,915

1	Regulatory	US	**5/14/2007**	Temp 110	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-186**	**S-186**	64,915
1	Regulatory	US	**5/8/2007**	Temp 112	FDA Submission - IND	**Protocol Amendment. Change to Protocol: Addendum to Protocol(s) AMB-320/321-E, AMB-222 and AMB-220-E. S-185**	**S-185**	64,915
1	Regulatory	US	**5/2/2007**	Temp 110	FDA Submission - IND	**Protocol Amendment. New Protocol and New Investigator. S-184**	**S-184**	64,915
1	Regulatory	US	**4/30/2007**	Temp 110	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Report. S-183**	**S-183**	64,915
1	Regulatory	US	**4/27/2007**	Temp 110	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Report. S-182**	**S-182**	64,915
1	Regulatory	US	**4/26/2007**	Book 109	FDA Submission - IND	**Protocol Amendment. New Investigators. S-181**	**S-181**	64,915
1	Regulatory	US	**4/24/2007**	Book 109	FDA Submission - IND	**Protocol Amendment. Change to Protocol: Replacement of Amendment No. 1.0 to Protocol AMB-323. S-180**	**S-180**	64,915
1	Regulatory	US	**4/11/2007**	Book 109	FDA Submission - IND	**IND Safety Report – Initial Written Report. S-179**	**S-179**	64,915
1	Regulatory	US	**4/10/2007**	Book 109	FDA Submission - IND	**Protocol Amendment. New Protocol and New Investigator. S-178**	**S-178**	64,915
1	Regulatory	US	**4/4/2007**	Book 109	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Report. S-177**	**S-177**	64,915
1	Regulatory	US	**3/22/2007**	Temp 111	FDA Submission - IND	**Protocol Amendment. Change to Protocol: Amendment No. 1 to Protocol AMB-323. S-176**	**S-176**	64,915
1	Regulatory	US	**3/21/2007**	Book 109	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-175**	**S-175**	64,915
1	Regulatory	US	**2/23/2007**	Book 109	FDA Submission - IND	**Protocol Amendment. New Investigators. S-174**	**S-174**	64,915
1	Regulatory	US	**2/23/2007**	Book 109	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Report. S-173**	**S-173**	64,915
1	Regulatory	US	**2/23/2007**	Book 109	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-172**	**S-172**	64,915
1	Regulatory	US	**2/15/2007**	Book 109	FDA Submission - IND	**IND Safety Report. Follow-up to written Report. S-171**	**S-171**	64,915

1	Regulatory	US	2/2/2007	Book 109	FDA Correspondence - Email	E.Smith/L.Tanner - Following on Transfer of Sponsorship from Myogen to Gilead, Sciences	2007-02-02_64915_CORR_EMAIL_ESMITH_LTANNER.pdf	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-170**	S-170	64,915
1	Regulatory	US	1/30/2007	Book 109	FDA Submission - IND	**Protocol Amendment. New Investigators. S-169**	S-169	64,915
1	Regulatory	US	1/25/2007	Book 109	FDA Submission - IND	**Protocol Amendment. New Protocol and New Investigator. S-168**	S-168	64,915
1	Regulatory	US	12/19/2006	Book 83	FDA Submission - IND	**Protocol Amendment. New Investigators. S-167**	S-167	64,915
1	Regulatory	US	12/15/2006	Book 83	FDA Correspondence - Letter	E.Fromm/L.Tanner. FDA Letter - Acknowledgment of the sponsor change.	2006-12-15_64915_CORR_LETTER_EFROMM_LTANNER.pdf	64,915
1	Regulatory	US	12/12/2006	Book 83	FDA Correspondence - Phone	L.Tanner/M.Robb. FDA contact report (phone call) - Clarify process for liaison with the Division during the review of NDA 022-081 and for submitting responses to reviewer questions.	2006-12-12_64915_CORR_PHONE_MROBB_LTANNER_.pdf	64,915
1	Regulatory	US	12/8/2006	Book 83	FDA Correspondence - Letter	N.Stockbridge/L.Tanner. FDA Letter indicates that Division does not recommend use of proprietary name LETAIRIS.	2006-12-08_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	12/7/2006	Book 83	FDA Correspondence - Letter	N.Stockbridge/L.Tanner. FDA Letter - Clarification to Requirements 120-day Safety Update	2006-12-07_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	12/7/2006	Book 83	FDA Submission - IND	**Other. Transfer of Sponsorship. S-165**	S-166	64,915
1	Regulatory	US	12/6/2006	Book 83	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm status of submission of NDA and transfer of sponsorship from Myogen to Gilead Sciences, Inc.	2006-12-06_64915_CORR_PHONE_MROBB_LTANNER_.pdf	64,915
1	Regulatory	US	11/28/2006	Book 83	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-165**	S-165	64,915
1	Regulatory	US	11/20/2006	Book 83	FDA Submission - IND	**Protocol Amendment. New Investigators. S-164**	S-164	64,915
1	Regulatory	US	11/20/2006	Book 83	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-163**	S-163	64,915

1	Regulatory	US	**11/7/2006**	Book 83	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-162**	**S-162**	64,915
1	Regulatory	US	**10/30/2006**	Book 83	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-161**	**S-161**	64,915
1	Regulatory	US	**10/24/2006**	Book 83	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm how RiskMAP materials are regulated and obtain status of review of trademark.	**2006-10-24_64915_CORR_PHONE_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**10/20/2006**	Book 83	FDA Submission - IND	**Protocol Amendment. New Investigators. S-160**	**S-160**	64,915
1	Regulatory	US	**10/20/2006**	Book 83	FDA Correspondence - Email	L.Tanner/M.Robb - FDA contact report (e-mail) - Proposal for 4-month Safety Update to NDA, S-159	**2006-10-20_64915_CORR_EMAIL_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**10/16/2006**	Book 83	FDA Correspondence - Email	L.Tanner/M.Robb - FDA contact report (e-mail) that confirms that the word version of the PI needs to be submitted in the two-column format.	**2006-10-16_64915_CORR_EMAIL_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**10/13/2006**	Book 83	FDA Submission - IND	**Other: Proposal for 4-Month Safety Update. S-159**	**S-159**	64,915
1	Regulatory	US	**10/12/2006**	Book 83	FDA Correspondence - Email	L.Tanner/M.Rabb. Email with two attachments. Clarification on Format of PI; 1vs. 2 Column Format for the PI; Ambrisentan.	**2006-10-12_64915_CORR_EMAIL_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**10/10/2006**	Book 83	FDA Correspondence - Email	Email from T.Marshall to S. Goldie with the attachment - electronic Desk Copy of AMB S-157: New Commercial Drug Product Dissolution Method.	**2006-10-10_64915_CORR_EMAIL_TMARSHALL_SGOLDIE_.pdf**	64,915
1	Regulatory	US	**10/9/2006**	Book 83	FDA Submission - IND	**IND Safety Report. Initial and Follow-up Written Report. S-158**	**S-158**	64,915
1	Regulatory	US	**10/6/2006**	Book 83	FDA Submission - IND	**Other: CMC - Proposed Commercial Dissolution Method. S-157**	**S-157**	64,915
1	Regulatory	US	**10/4/2006**	Book 83	FDA Correspondence - Email	Email from M. Robb to L. Tanner. Subject: Pediatric exclusivity, Orphan Drugs; Ambrisentan - ND 22-081.	**2006-10-04_64915_CORR_EMAIL_LTANNER_MROBB_.pdf**	64,915

1	Regulatory	US	10/4/2006	Book 83	FDA Correspondence - Phone	M.Robb/L.Tanner. Purpose: Confirm location for providing the statement that ambrisentan is exempt from the requirement for submitting pediatric data in the NDA.	2006-10-04_64915_CORR_PHONE_MROBB_LTANNER_.pdf	64,915
1	Regulatory	US	9/27/2006	Book 83	FDA Correspondence - Phone	M.Robb/L.Tanner. Purpose: Confirm timing for the submission of NDA.	2006-09-27_64915_CORR_PHONE_MROBB_LTANNER_.pdf	64,915
1	Regulatory	US	9/26/2006	Book 82	FDA Submission - IND	**Protocol Amendment. New Investigators. S-156**	S-156	64,915
1	Regulatory	US	9/12/2006	Book 82	FDA Submission - IND	**IND Safety Report. Initial and Follow-up Written Report. S-155**	S-155	64,915
1	Regulatory	US	9/6/2006	Book 82	FDA Submission - IND	**Protocol Amendment AMB-323. New Investigators. S-154**	S-154	64,915
1	Regulatory	US	8/23/2006	Book 82	FDA Correspondence - Letter - Meeting Minutes	Letter from S.Goldie/T.Marshall Meeting Minutes - Pre-NDA CMC meeting with FDA.	2006-08-23_64915_CORR_MEETING_MINUTES.pdf	64,915
1	Regulatory	US	8/21/2006	Book 82	FDA Correspondence - Email	Email from the FDA User Fee System	2006-08-21_64915_CORR_EMAIL_USERFEESFDA_HISOKOSKI_.pdf	64,915
1	Regulatory	US	8/8/2006	Book 82	FDA Correspondence - Phone	L.Tanner/M.Robb. Call at 2:30 PM. Purpose: Confirm Format of Annotating Prescribing Information.	2006-08-08_64915_CORR_PHONE_MROBB_LTANNER_2.pdf	64,915
1	Regulatory	US	8/8/2006	Book 82	FDA Correspondence - Phone	L.Tanner/M.Robb. Call at 8:30AM Purpose: Confirm format of annotating the prescribing information based on the new requirements.	2006-08-08_64915_CORR_PHONE_MROBB_LTANNER_.pdf	64,915
1	Regulatory	US	7/26/2006	Book 82	FDA Correspondence - Mating Minutes	T.Marshall. Myogen Pre-NDA CMC Meeting Minutes for July 26, 2006.	2006-07-26_64915_CORR_MEETING_MINUTES.pdf	64,915
1	Regulatory	US	7/25/2006	Book 82	FDA Submission - IND	**Protocol Amendment. New Investigators. S-153**	S-153	64,915
1	Regulatory	US	7/24/2006	Book 82	FDA Correspondence - Email	T.Marshall/S.Goldie. FDA Pre-meeting Responses to Myogen's Pre-NDA CMC Meeting Questions.	2006-07-24_64915_CORR_EMAIL_TMARSHALL_SGOLDIE_1.pdf	64,915
1	Regulatory	US	7/24/2006	Book 82	FDA Correspondence - Email	T.Marshall/S.Goldie. Pre-NDA CMC Meeting - Additional Attendees.	2006-07-24_64915_CORR_EMAIL_TMARSHALL_SGOLDIE.pdf	64,915
1	Regulatory	US	7/17/2006	Book 82	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-152**	S-152	64,915

1	Regulatory	US	**7/13/2006**	Book 82	FDA Correspondence - Phone	H.Isokoski/B.Friedman. NDA Number for Ambrisentan.	**2006-07-12_64915_CORR_PHONE_HISOKOSKI_BFRIEDMAN_.pdf**	64,915
1	Regulatory	US	**7/6/2006**	Book 82	FDA Correspondence - Email	L.CURRAN/ESUB/FDA. To clarify issues to which there is no apparent guidance.	**2006-07-06_64915_CORR_EMAIL_ESUB_LCURRAN.pdf**	64,915
1	Regulatory	US	**7/6/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Safety Report. S-151**	**S-151**	64,915
1	Regulatory	US	**6/30/2006**	Book 107-108	FDA Submission - IND	**Annual Report. S-150**	**S-150**	64,915
1	Regulatory	US	**6/28/2006**	Book 106	FDA Submission - IND	**Other. CMC Pre-NDA Information Package S-149**	**S-149**	64,915
1	Regulatory	US	**6/20/2006**	Book 82	FDA Submission - IND	**Information Amendment. Update to Investigator 1572 Forms. S-148**	**S-148**	64,915
1	Regulatory	US	**6/20/2006**	Book 82	FDA Correspondence - Phone	L.Tanner/M.Rabb. Feedback on proposed plan for submitting carcinogenicity data to the NDA (IND Serial No. 145).	**2006-06-20_64915_CORR_PHONE_MROBB_LTANNER_.pdf**	64,915
1	Regulatory	US	**6/20/2006**	Book 105	FDA Submission - IND	**Information Amendment. New Protocol and New Investigator. S-147**	**S-147**	64,915
1	Regulatory	US	**6/15/2006**	Book 100-104	FDA Submission - IND	**Information Amendment -Clinical CSRs AMB-105 and AMB-106. S-146**	**S-146**	64,915
1	Regulatory	US	**6/14/2006**	Book 82	FDA Correspondence - Phone	Phone. T.Marshall/S.Goldie regarding Pre-NDA CMC Meeting. Scheduling Submission of Pre-NDA CMC meeting information.	**2006-06-14_64915_CORR_PHONE_SGOLDIE_TMARSHALL.pdf**	64,915
1	Regulatory	US	**6/14/2006**	Book 82	FDA Correspondence - Email	Email from L.Tanner/M.Robb - Request for feedback: IND64,915 S-145.	**2006-06-14_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**6/14/2006**	Book 82	FDA Submission - IND	**Other. Request Feedback on Nonclinical NDA Format and Content. S-145**	**S-145**	64,915
1	Regulatory	US	**6/12/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Initial and Follow-up Written Report. S-144**	**S-144**	64,915
1	Regulatory	US	**6/2/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-143**	**S-143**	64,915
1	Regulatory	US	**6/1/2006**	Book 82	FDA Submission - IND	**Information Amendment. Update to Investigator 1572 Forms. S-142**	**S-142**	64,915

1	Regulatory	US	**5/26/2006**	Book 82	FDA Correspondence - Letter	Letter from S.Goldie/T.Marshall regarding Pre-NDA CMC meeting with FDA.	**2006-05-26_64915_CORR_LETTER_SGOLDIE_TMARSHALL.pdf**	64,915
1	Regulatory	US	**5/26/2006**	Book 82	FDA Correspondence - Fax	Fax from M.Robb/L.Tanner - Meeting Minutes from Pre-NDA meeting with FDA on May 19, 2006.	**2006-05-26_64915_CORR_FAX_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**5/26/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Follow-up to a Written Report. S-141**	**S-141**	64,915
1	Regulatory	US	**5/25/2006**	Book 82	FDA Correspondence - Email	S.Goldie/T.Marshall. Contract Information.	**2006-05-25_64915_CORR_EMAIL_TMARSHALL_SGOLDIE.pdf**	64,915
1	Regulatory	US	**5/25/2006**	Book 82	FDA Correspondence - Phone	Phone call - T.Marshall/S.Goldie regarding Pre-NDA CMC meeting request.	**2006-05-25_64915_CORR_PHONE_SGOLDIE_TMARSHALL.pdf**	64,915
1	Regulatory	US	**5/19/2006**	Book 82	FDA Correspondence - Phone	Phone call - T.Marshall/M.Robb regarding Pre-NDA CMC meeting request.	**2006-05-19_64915_CORR_PHONE_MROBB_TMARSHALL.pdf**	64,915
1	Regulatory	US	**5/19/2006**	Book 82	FDA Correspondence - Email	Email - T.Marshall/S.Goldie regarding Pre-NDA CMC meeting. IND Submission S-139 attached.	**006-05-19_64915_CORR_EMAIL_TMARSHALL_SGOLDIE.pdf**	64,915
1	Regulatory	US	**5/18/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-140**	**S-140**	64,915
1	Regulatory	US	**5/17/2006**	Book 82	FDA Correspondence - Email	Email - L.Tanner/M.Robb. To discuss comments and questions (pre-NDA meeting with FDA).	**2006-05-17_64915_CORR_EMAIL_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**5/17/2006**	Book 82	FDA Submission - IND	**Other. Type B Meeting Request: Pre-NDA CMC. S-139**	**S-139**	64,915
1	Regulatory	US	**5/8/2006**	Book 82	FDA Correspondence - Email	L.Tanner/M.Robb - Response to FDA comment (SN#138) regarding scoop and content of NDA.	**2006-05-08_64915_CORR_EMAIL_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**5/8/2006**	Book 82	FDA Submission - IND	**Other: Response to FDA Comments. S-138**	**S-138**	64,915
1	Regulatory	US	**5/5/2006**	Book 82	FDA Correspondence - Phone	Phone call - L.Tanner/M.Rabb to discuss status of written comments to questions in pre-NDA briefing document (IND Serial No.134)	**2006-05-05_64915_CORR_PHONE_MROBB_LTANNER_1.pdf**	64,915

1	Regulatory	US	**5/5/2006**	Book 82	FDA Correspondence - Phone	Phone call - L.Tanner/M.Rabb. Myogen response to Division comments on IND Serial No. 127; date of internal meeting; clarify FDA position on use of audio-visual aids.	**2006-05-05_64915_CORR_PHONE_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**5/4/2006**	Book 97-99	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology. S-137**	**S-137**	64,915
1	Regulatory	US	**4/27/2006**	Book 82	FDA Submission - IND	**Protocol Amendment. New Investigators Update. S-136**	**S-136**	64,915
1	Regulatory	US	**4/27/2006**	Book 82	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-135**	**S-135**	64,915
1	Regulatory	US	**4/21/2006**	Book 96	FDA Submission - IND	**Other: Pre-NDA Briefing Document. S-134**	**S-134**	64,915
1	Regulatory	US	**4/21/2006**	Book 82	FDA Correspondence - Multiple	Purpose: To test system upgrade and functionality in advance of actual Ambrisentan eCTD.	**2006-04-21_64915_CORR_MULTIPLE_LCURRAN_CDER_ESUB.pdf**	64,915
1	Regulatory	US	**4/20/2006**	Book 82	FDA Correspondence - Letter	The response to the questions regarding the NDA that was submitted in IND Serial No. 127	**2006-04-20_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**4/19/2006**	Book 92-95	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology. S-133**	**S-133**	64,915
1	Regulatory	US	**4/19/2006**	Book 81	FDA Submission - IND	**Other: Population Pharmacokinetic (PK) Data Analysis Plan (DAP) Amendment. S-132**	**S-132**	64,915
1	Regulatory	US	**4/17/2006**	Book 81	FDA Correspondence - Phone	Phone call L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA submitted in S-127	**2006-04-17_64915_CORR_PHONE_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**4/11/2006**	Book 81	FDA Correspondence - Email	Email with the Word Attachment - L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA submitted in S-127	**2006-04-11_64915_CORR_EMAIL_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**4/11/2006**	Book 81	FDA Correspondence - Phone	Phone call L.Tanner/M.Robb regarding status of FDA responses to questions relative to the NDA submitted in S-127	**2006-04-11_64915_CORR_PHONE_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**4/5/2006**	Book 81	FDA Correspondence - Phone	Phone call - L.Tanner/N.Beasley regarding analysis of pharmacokinetic parameters vs. QTc interval assessments.	**2006-04-05_64915_CORR_PHONE_LTANNER_NBEASLEY.pdf**	64,915

1	Regulatory	US	**4/5/2006**	Book 91	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology. S-131**	**S-131**	64,915
1	Regulatory	US	**3/29/2006**	Book 81	FDA Submission - IND	**Protocol Amendment. New Investigators and Investigator Update. S-130**	**S-130**	64,915
1	Regulatory	US	**3/24/2006**	Book 81	FDA Submission - IND	**Information Amendment Pharmacology/Toxicology. S-129**	**S-129**	64,915
1	Regulatory	US	**3/23/2006**	Book 81	FDA Correspondence - Phone	Phone call, L.Tanner/M.Robb - Clarification of FDA participants for pre-NDA meeting scheduled May 19, 2006.	**2006-03-23_64915_CORR_PHONE_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**3/23/2006**	Book 89-90	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology. S-128**	**S-128**	64,915
1	Regulatory	US	**3/23/2006**	Book 81	FDA Correspondence - Email	E-mail from L.Tanner /M.Robb to obtain feedback from the statisticians on how to address their recommendations regarding the methodology used in the DAPs for the individual Phase 3 studies AMB-320 and AMB-321.	**2006-03-23_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**3/21/2006**	Book 81	FDA Correspondence - Phone	Phone call, L.Tanner/M.Robb - Clarification of FDA participants for pre-NDA meeting scheduled May 19, 2006.	**2006-03-21_64915_CORR_PHONE_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**3/20/2006**	Book 81	FDA Correspondence - Fax	Fax from M.Robb/L.Tanner regarding Pre-NDA meeting conformation with FDA on May 19, 2006.	**2006-03-20_64915_CORR_FAX_MROBB_LTANNER.pdf**	64,915
1	Regulatory	US	**3/16/2006**	Book 81	FDA Correspondence - Letter	Letter from N.Stockridge/L.Tanner - Comments (Clinical Pharmacology and Biopharmaceutics) on AMB submission.	**2006-03-16_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**3/15/2006**	Book 81	FDA Submission - IND	**Other. Requirements and Format of NDA. S-127**	**S-127**	64,915
1	Regulatory	US	**3/15/2006**	Book 81	FDA Correspondence - Email	L.Tanner/M.Robb - Email regarding IND 64,915; Serial No. 127; Requirements and Format of NDA.	**2006-03-15_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**3/14/2006**	Book 81	FDA Correspondence - Letter	Letter from N.Stockridge/L.Tanner with the comments on AMB submission.	**2006-03-14_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**3/14/2006**	Book 81	FDA Correspondence - Email	L.Curran/K.Edmunds - Email regarding Pilot Submission.	**2006-03-14_64915_CORR_EMAIL_LCURRAN_KEDMUNDS.pdf**	64,915

1	Regulatory	US	**3/10/2006**	Book 81	FDA Correspondence - Phone call	L.Tanner/M.Robb phone call regarding feedback on : submission of the rat carcinogenicity, acceptability of cross-reference to NDA in the IND Annual Report, notification of submission with questions on scope, format and date of pre-NDA meeting.	**2006-03-10_63412_CORR_PHONE_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**3/8/2006**	Book 81	FDA Submission - IND	**Other: Type B Meeting Request: Pre-NDA. S-126**	**S-126**	64,915
1	Regulatory	US	**3/2/2006**	Book 81	FDA Submission - IND	**Protocol Amendment. New investigators and 1572 Update. S-125**	**S-125**	64,915
1	Regulatory	US	**3/2/2006**	Book 81	FDA Submission - IND	**IND Safety Report. Follow-up to a Fax Report: 52597. S-124**	**S-124**	64,915
1	Regulatory	US	**2/27/2006**	Book 81	FDA Correspondence - Phone call/Fax	L.Curran called M.Robb to inform her that he would be faxing a 7-Day Safety Report. Faxed 7-Day Safety Report.	**2006-02-27_64915_CORR_PHONE_FAX_LCURRAN_MROBB.pdf**	64,915
1	Regulatory	US	**2/21/2006**	Book 81	FDA Submission - IND	**Other: Response to the IND correspondence. S-123**	**S-123**	64,915
1	Regulatory	US	**2/15/2006**	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge to L. Tanner regarding FDA approval for fast track designation.	**2006-02-15_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**2/9/2006**	Book 88	FDA Submission - IND	**Other. Request for Fast Track Designation. S-122**	**S-122**	64,915
1	Regulatory	US	**2/8/2006**	Book 81	FDA Correspondence - Letter	Letter from N.Stockbridge to L. Tanner regarding Myogen request for additional clarification to a letter dated 22 December 2005 regarding the changes to the statistical analysis plans that was reflected in the protocol amendments to AMB-320 and AMB-321.	**2006-02-08_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**2/8/2006**	Book 81	FDA Correspondence - Phone call	Phone call L.Tanner/M.Robb. Confirm whether the popPK DAP has been reviewed and whether Division comments will be forthcoming.	**2006-02-08_63412_CORR_PHONE_LTANNER_MROBB_.pdf**	64,915
1	Regulatory	US	**1/30/2006**	Book 81	FDA Correspondence - Phone call	Phone call - L.Tanner/B.N.Beasley regarding status of Clinical QT/QTc Study AMB-104	**2006-01-30_64915_CORR_PHONE_LTANNER_BNBEASLEY.pdf**	64,915

1	Regulatory	US	1/27/2006	Book 81	FDA Submission - IND	**IND Safety Report. Initial Written Report: 51629. Follow-Up to a Written Report: 52559. S-121**	**S-121**	64,915
1	Regulatory	US	1/26/2006	Book 87	FDA Submission - IND	**Protocol Amendment. Change in Protocol AMB-104. S-120**	**S-120**	64,915
1	Regulatory	US	1/25/2006	Book 81	FDA Submission - IND	**Protocol Amendment. New investigators and 1572 Update. S-119**	**S-119**	64,915
1	Regulatory	US	1/24/2006	Book 86	FDA Submission - IND	**Protocol Amendment. Change in Protocol AMB-222. S-118**	**S-118**	64,915
1	Regulatory	US	1/23/2006	Book 81	FDA Correspondence - Phone call	Phone call L.Tanner/M.Robb. Feedback on submitting additional documentation to support changes in the revised Protocol AMB-222 that was submitted in Serial No. 115	**2006-01-23_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	1/23/2006	Book 85	FDA Submission - IND	**Protocol Amendment. Change in Protocol AMB-107. S-117**	**S-117**	64,915
1	Regulatory	US	1/19/2006	Book 81	FDA Correspondence - Phone call	Phone call - L.Tanner/L.Velazquez regarding feedback on Bioequivalence Protocol AMB-103 submitted on 12/19/2005 S-108.	**2006-01-19_64915_CORR_PHONE_LTANNER_LVELAZQUEZ.pdf**	64,915
1	Regulatory	US	1/16/2006	Book 81	FDA Submission - IND	**IND Safety Report. Follow-up to a written Report: 52566. S-116**	**S-116**	64,915
1	Regulatory	US	1/13/2006	Book 84	FDA Submission - IND	**Protocol Amendment. Change in Protocol. S-115**	**S-115**	64,915
1	Regulatory	US	1/10/2006	Book 81	FDA Correspondence - Phone call	Phone call L.Tanner/M.Robb. Follow-up on clarification on FDA statistical comments to protocol amendments for AMB-320 and AMB-321.	**2006-01-10_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	1/9/2006	Book 81	FDA Submission - IND	**IND Safety Report. Follow-up to a written Report: 51627. S-114**	**S-114**	64,915
1	Regulatory	US	1/5/2006	Book 81	FDA Correspondence - Email	Email - M.Robb/L.Tanner regarding IND 64,915 Letairis trade name - Response to Questions.	**2006-01-05_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	1/4/2006	Book 81	FDA Submission - IND	**IND Safety Report. Initial Written Report. S-113**	**S-113**	64,915

1	Regulatory	US	12/2006	Book 81	FDA Correspondence - Email	Email - M.Robb/L.Tanner Clarification on Satisfied Comments S-084 and S-098, IND 64,915.	2006-01-02_64915_CORR_EMAIL_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	12/28/2005	Book 52	FDA Correspondence - Email	Email - M.Robb/L.Tanner regarding IND 64,915 Letairis trade name.	2005-12-28_64915_CORR_EMAIL_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	12/27/2005	Book 52	FDA Correspondence - Fax	The FDA minutes for the Type C meeting scheduled as a teleconference on 15 December 2005 to discuss the PK/PD development plan. Attached are Internal (Myogen) Minutes for the same meeting.	2005-12-27_64915_CORR_FAX_MTG_MINUTES_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	12/22/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L.Tanner regarding comments on ARIES-2 DAP.	2005-12-22_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf	64,915
1	Regulatory	US	12/21/2005	Book 52	FDA Correspondence - Phone call	Phone call on 12-20-2005 and 12-21-2005 L.Tanner/M.Robb. Intent to submit application for fast track designation.	2005-12-21_64915_CORR_PHONE_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	12/21/2005	Book 52	FDA Submission - IND	**IND Safety Report. Initial Written Report: 51627. S-112**	S-112	64,915
1	Regulatory	US	12/21/2005	Book 52	FDA Submission - IND	**IND Safety Report. Initial Written Report: 52559. S-111**	S-111	64,915
1	Regulatory	US	12/20/2005	Book 80	FDA Submission - IND	**Protocol Amendment. New Protocol (AMB-107) and New Investigator. S-110**	S-110	64,915
1	Regulatory	US	12/19/2005	Book 52	FDA Correspondence - Email	ECG measurements on Baseline and Treatment Days in Protocol AMB-104.	2005-12-19_64915_CORR_EMAIL_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	12/19/2005	Book 52	FDA Submission - IND	**IND Safety Report. Initial Written Report: 52555. S-109**	S-109	64,915
1	Regulatory	US	12/19/2005	Book 79	FDA Submission - IND	**Protocol Amendment. New Protocol (AMB-103) and New Investigators. S-108**	S-108	64,915
1	Regulatory	US	12/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. T.Marshall/M.Robb. Feedback from Ambrisentan Chemistry Reviewer for Drug Substance and Drug Product IND Amendments.	2005-12-19_64915_CORR_PHONE_TMARSHALL_MROBB.pdf	64,915
1	Regulatory	US	12/16/2005	Book 52	FDA Correspondence - Phone call	Phone call. T.Marshall/M.Robb. Request Feedback from Ambrisentan Chemistry Reviewer for Drug Product Update.	2005-12-16_64915_CORR_PHONE_TMARSHALL_MROBB.pdf	64,915

1	Regulatory	US	**12/15/2005**	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: List of Myogen Participants Type C Meeting 12/15/2005.	**2005-12-15_64915_CORR_EMAIL_LTANNER_MROBB_1.pdf**	64,915
1	Regulatory	US	**12/15/2005**	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Clarification on Medical Review Comments QT/QTc Protocol AMB-104.	**2005-12-15_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/14/2005**	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Slides Top Line Results Phase 3 Study AMB-321; IND 64,915 Ambrisentan.	**2005-12-14_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/14/2005**	Book 52	FDA Correspondence - Phone call	Phone call from L. Tanner to M. Robb. Subject: Type C teleconference meeting scheduled 12/15/05; QT/QTc Study (AMB-104)	**2005-12-14_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/13/2005**	Book 52	FDA Correspondence - Email	Email - L. Tanner/M.Robb. Conformation of FDA Participants Teleconference - 12/15/2005.	**2005-12-13_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/12/2005**	Book 52	FDA Correspondence - Phone call	Phone call (on 12/09/05 and 12/12/05) from L. Tanner to M. Robb. Subject: Clarify FDA participations Type C teleconference meeting scheduled 12/15/2005.	**2005-12-12_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/6/2005**	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Ambrisentan Type C Meeting: Myogen Participants and Teleconference Instruction.	**2005-12-06_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/1/2005**	Book 52	FDA Correspondence - Email	Email - L.Tanner/M.Robb. Subject: Electronic Copy of S-106 - Analysis Plan for Population Pharmacokinetic Modeling.	**2005-12-01_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**12/1/2005**	Book 73-78	FDA Submission - IND	**Information Amendment. Clinical Study Report EE002. S-107**	**S-107**	64,915
1	Regulatory	US	**12/1/2005**	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: To confirm receipt of desk copies of PK/PD briefing package for the teleconference meeting scheduled 15 December 2005 and update on IND submissions this week.	**2005-12-01_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**11/30/2005**	Book 52	FDA Submission - IND	**Other: Data Analysis Plan for Population Pharmacokinetic Modeling. S-106**	**S-106**	64,915

1	Regulatory	US	**11/30/2005**	Book 72	FDA Submission - IND	**Other: Briefing Document for Type c Meeting. S-105**	**S-105**	64,915
1	Regulatory	US	**11/30/2005**	Book 71	FDA Submission - IND	**Protocol. New Protocol and New Investigator. S-104**	**S-104**	64,915
1	Regulatory	US	**11/30/2005**	Book 70	FDA Submission - IND	**Other: Data Analysis Plans. S-103**	**S-103**	64,915
1	Regulatory	US	**11/29/2005**	Book 69	FDA Submission - IND	**Other: Data Analysis Plans. S-102**	**S-102**	64,915
1	Regulatory	US	**11/29/2005**	Book 65-68	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology. S-101**	**S-101**	64,915
1	Regulatory	US	**11/28/2005**	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Myogen response to FDA comments on the QT/QTc study design (Serial No. 096)	**2005-11-28_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**11/28/2005**	Book 64	FDA Submission - IND	**Other. Data Analysis Plan. S-100**	**S-100**	64,915
1	Regulatory	US	**11/23/2005**	Book 63	FDA Submission - IND	**Protocol Amendment. New Investigators. S-099**	**S-099**	64,915
1	Regulatory	US	**11/16/2005**	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: Instruction for shipping PK/PD package for the teleconference meeting scheduled 12/15/2005.	**2005-11-16_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**11/14/2005**	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb. Purpose: To confirm timing of submitting the PK/PD briefing package for the teleconference meeting scheduled 15 December 2005.	**2005-11-14_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**11/11/2005**	Book 62	FDA Submission - IND	**Protocol Amendment. Change in Protocol. Information Amendment Clinical. S-098**	**S-098**	64,915
1	Regulatory	US	**11/11/2005**	Book 52	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology 2-Year Rat and Mouse Carcinogenicity Studies. S-097**	**S-097**	64,915
1	Regulatory	US	**11/10/2005**	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/W.Link on 11/10/05 and 11/09/05 regarding 2 year carcinogenicity (CAC) studies in mice and rats.	**2005-11-10_64915_CORR_PHONE_LTANNER_WLINK.pdf**	64,915

1	Regulatory	US	11/9/2005	Book 52	FDA Correspondence - Phone call	Phone call - L.Tanner/M.Robb on 11/08/05 and 11/09/05 regarding 2 year carcinogenicity (CAC) studies in mice and rats. Arrange teleconference with Dr. William Link to provide survival update on CAC studies.	**2005-11-09_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	11/7/2005	Book 52	FDA Submission - IND	**Other: Response to FDA Comments on QT/QTc Study Design. S-096**	**S-096**	64,915
1	Regulatory	US	11/4/2005	Book 61	FDA Submission - IND	**Protocol. New Protocol and New Investigator. S-095**	**S-095**	64,915
1	Regulatory	US	11/4/2005	Book 52	FDA Submission - IND	**Other: Trademark Evaluation. S-094**	**S-094**	64,915
1	Regulatory	US	10/24/2005	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding minutes from October 19, 2005 teleconference.	**2005-10-24_64915_CORR_EMAIL_RFORTNEY_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	10/21/2005	Book 60	FDA Submission - IND	**Protocol Amendment: New Investigators. Other: Revisions to FDA Forms 1572. S-093**	**S-093**	64,915
1	Regulatory	US	10/20/2005	Book 52	FDA Correspondence - Phone call	Phone call form L. Weissberger to M. Robb. Subject: QT/QTc study - comments on study design submitted for both darusentan (Serial No. 076) and ambrisentan (Serial No. 086)	**2005-10-20_64915_CORR_PHONE_LWEISSBEGER_MROBB.pdf**	64,915
1	Regulatory	US	10/19/2005	Book 52	FDA Correspondence - Letter	Letter from R. Fortney to L. Weissberger. Teleconference Minutes from FDA and Internal Minutes - October 19, 2005.	**2005-10-19_64915_CORR_LETTER_RFORTNEY_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	10/19/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to R. Fortney regarding teleconference on October 19, 2005.	**2005-10-19_64915_CORR_EMAIL_RFORTNEY_LTANNER.pdf**	64,915
1	Regulatory	US	10/18/2005	Book 52	FDA Submission - IND	**Protocol. New Protocol and New Investigator. S-092**	**S-092**	64,915
1	Regulatory	US	10/13/2005	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding FDA letter with comments on QT/QTc Study.	**2005-10-13_64915_CORR_EMAIL_RFORTNEY_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	10/12/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Weissberger. Comments on QT/QTc study proposal for Ambrisentan.	**2005-10-12_64915_CORR_LETTER_NSTOCKBRIDGE_LWEISSBERGER.pdf**	64,915

1	Regulatory	US	**10/12/2005**	Book 52	FDA Correspondence - Phone call	Phone call. L. Tanner/R. Fortney. Subject: Teleconference DAP; S-084	**2005-10-12_64915_CORR_PHONE_LTANNER_RFORTNEY.pdf**	64,915
1	Regulatory	US	**10/12/2005**	Book 52	FDA Correspondence - Email	Email from L. Tanner to R. Fortney regarding Teleconference on 10/19/2005, additional participant.	**2005-10-12_64915_CORR_EMAIL_RFORTNEY_LTANNER.pdf**	64,915
1	Regulatory	US	**10/11/2005**	Book 52	FDA Correspondence - Phone call	Phone call. L. Tanner/R. Fortney. L. Tanner called R. Fortney on 10/06/05, 10/10/05 and 10/11/05. Subject: Teleconference DAP; S-084	**2005-10-11_64915_CORR_PHONE_LTANNER_RFORTNEY.pdf**	64,915
1	Regulatory	US	**10/11/2005**	Book 52	FDA Correspondence - Email	Email from R. Fortney to L. Weissberger regarding QT Study Comments.	**2005-10-11_64915_CORR_EMAIL_RFORTNEY_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	**10/5/2005**	Book 52	FDA Correspondence - Phone call	Phone call. L. Tanner/R. Fortney. Subject: Reschedule Type C Meeting; S-087	**2005-10-05_64915_CORR_PHONE_LTANNER_RFORTNEY.pdf**	64,915
1	Regulatory	US	**10/4/2005**	Book 59	FDA Submission - IND	**Information Amendment. Chemistry, Manufacturing, and Controls. S-091**	**S-091**	64,915
1	Regulatory	US	**10/4/2005**	Book 52	FDA Submission - IND	**IND Safety Report: Follow-up to a Written Report. S-090**	**S-090**	64,915
1	Regulatory	US	**10/4/2005**	Book 52	FDA Correspondence - Phone call	Phone call. L. Tanner/R. Fortney. Subject: Intention to Cancel or Re-schedule Type C Meeting; Serial No. 087	**2005-10-04_64915_CORR_PHONE_LTANNER_RFORTNEY.pdf**	64,915
1	Regulatory	US	**9/28/2005**	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Tanner regarding FDA Division comments on the Data Analysis Plan for AMB-321.	**2005-09-28_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	**9/26/2005**	Book 58	FDA Submission - IND	**Protocol Amendment: New Investigators: Gabbay, Channick, Frost, Waxman, Sulica, Taichman, Olschewski, Souza, Pulido, Rivera, Swisher, Booth, Ross, White. S-089**	**S-089**	64,915
1	Regulatory	US	**9/21/2005**	Book 52	FDA Correspondence - Fax	Fax from M. Robb to L. Tanner. Subject: Conformation of 11/08/2005 Teleconference.	**2005-09-21_64915_CORR_FAX_MROBB_LTANNER.pdf**	64,915

1	Regulatory	US	9/20/2005	Book 52	FDA Correspondence - Phone call	Phone call L.Tanner/M.Robb. Finalize Date/Time of Type C Teleconference/Meeting. (Serial No.087); Status of DAP (Serial No. 084)	**2005-09-20_64915_CORR_PHONE_LTANNER_ROBBM.pdf**	64,915
1	Regulatory	US	9/19/2005	Book 52	FDA Correspondence - Phone call	Phone call T. Marshall/M.Robb. Subject: Follow-up to determine if Chemistry reviewer has any concerns regarding the drug substance IND update: IND 64,915, Serial No. 083, 4 Aug 05.	**2005-09-19_64915_CORR_PHONE_TMARSHALL_MROBB.pdf**	64,915
1	Regulatory	US	9/19/2005	Book 52	FDA Correspondence - Phone call	Phone call L.Tanner/M.Robb. Finalize Date/Time of Type C Teleconference/Meeting. (Serial No.087); Status of DAP (Serial No. 084)	**2005-09-19_64915_CORR_PHONE_LTANNER_ROBBM.pdf**	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Letter	Letter from N. Stockbridge to L. Tanner. Conformation that Food Effect Study Does not Need to be Repeated	**2005-09-15_64915_CORR_LETTER_NSTOCKBRIDGE_LTANNER.pdf**	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Submission - IND	**Information Amendment. Pharmacology/Toxicology 2-year Rat and Mouse Carcinogenicity Studies. S-088**	**S-088**	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Phone call	Phone called (1:30 p.m.) from L. Tanner to M. Robb regarding proposed Date for Type C Meeting PK/PD.	**2005-09-15_64915_CORR_PHONE_LTANNER_ROBBM.pdf**	64,915
1	Regulatory	US	9/15/2005	Book 52	FDA Correspondence - Phone call	Phone called (10:00 a.m.) from M. Robb to L. Tanner regarding proposed Date for Type C Meeting PK/PD.	**2005-09-15_64915_CORR_PHONE_LTANNER_ROBBM_2.pdf**	64,915
1	Regulatory	US	9/12/2005	Book 52	FDA Correspondence - Email	Email from L. Tanner to M.Robb regarding a Type C Meeting Request. S-087. Submission included.	**2005-09-12_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	9/12/2005	Book 52	FDA Submission - IND	**Other: Type C Meeting Request, Development Plan for Biopharmaceutics and Clinical Pharmacology. S-087**	**S-087**	64,915
1	Regulatory	US	9/7/2005	Book 52	FDA Submission - IND	**Other: Request for FDA Review of QT/QTc Study Proposal. S-086**	**S-086**	64,915

1	Regulatory	US	9/7/2005	Book 52	FDA Correspondence - Phone call	Phone call. L.Tanner/M.Robb. Subject: request to Submit QT/QTc Study Proposal to IND.	2005-09-07_64915_CORR_PHONE_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	8/31/2005	Book 52	FDA Correspondence - Email	Email from L.Weissberger to M.Robb regarding a summary of the QT/QTC evaluation proposing for Ambrisentan (64,915) and Darusentan (59,669).	2005-08-31_64915_CORR_EMAIL_WEISSBERGERL_ROBBM.pdf	64,915
1	Regulatory	US	8/25/2005	Book 52	FDA Submission - IND	**IND Safety Reports. S-085**	S-085	64,915
1	Regulatory	US	8/24/2005	Book 52	FDA Correspondence - Phone call	Phone call. M. Robb/L. Tanner. Subject: FDA Decision that Food Effect Study Does not Need to Be Repeated	2005-08-24_64915_CORR_PHONE_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	8/23/2005	Book 52	FDA Correspondence - Phone call	Phone call from M. Robb to L. Tanner. Subject: Clarify 7-day SAE Process for IND 63,412; Confirm FDA receipt of PDF file for Serial No. 084 (IND 64,915); Status of Serial No. 082 Food Effect (64, 915); Potential meeting PK/PD development plan (IND 64,915)	2005-08-23_64915_CORR_PHONE_MROBB_LTANNER.pdf	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Submission - IND	**Other: Data Analysis Plan (AMB-321) for FDA Feedback. S-084**	S-084	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Correspondence - Phone call	Phone call from L. Tanner to M. Robb. Subject: Clarify 7-day SAE Process; Status of Serial No. 082 Food Effect; Notification of DAP Submission.	2005-08-22_64915_CORR_PHONE_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	8/22/2005	Book 52	FDA Correspondence - Fax	Fax from L. Tanner to M. Robb. Subject: 7 Day Safety Report - Initial Manufacturer's Report No. 52505.	2005-08-22_64915_CORR_FAX_LTANNER_MROBB.pdf	64,915
1	Regulatory	US	8/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. From M. Cooper to T. Marshall. Subject: Division feedback on ambrisentan starting materials (IND 64,915, Serial No. 083)	2005-08-19_64915_CORR_PHONE_MCOOPER_TMARSHALL.pdf	64,915
1	Regulatory	US	8/19/2005	Book 52	FDA Correspondence - Phone call	Phone call. From T. Marshall to M. Robb. On 8/18/2005 T. Marshall left voice message and on 8/19/2005 phoned M. Robb. Subject: Follow-up on requested feedback on starting materials from IND 64,915, Serial No. 083 dated 08/04/2005.	2005-08-19_64915_CORR_PHONE_TMARSHALL_MROBB.pdf	64,915

1	Regulatory	US	**8/4/2005**	Book 57	FDA Submission - IND	**Information Amendment: Chemistry, Manufacturing and Controls. S-083**	**S-083**	64,915
1	Regulatory	US	**8/4/2005**	Book 52	FDA Correspondence - Phone call	Phone call from L.Tanner to M.Robb. Subject: Confirm submission of S-082 Formulations Food/Effect.	**2005-08-04_64915_CORR_PHONE_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**8/4/2005**	Book 52	FDA Correspondence - Phone call	Phone call from T. Marshall to M.Robb. Left phone message. Subject: Informed Project Manager of Drug Substance CMC Information Amendment and Requested Feedback on Starting Materials.	**2005-08-04_64915_CORR_PHONE_TMARSHALL_MROBB.pdf**	64,915
1	Regulatory	US	**8/4/2005**	Book 52	FDA Correspondence - Email	Email from L. Tanner to M.Robb regarding submission S-082. Submission included.	**2005-08-04_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**8/3/2005**	Book 52	FDA Submission - IND	**Response To FDA Request For Information. S-082**	**S-082**	64,915
1	Regulatory	US	**7/26/2005**	Book 56	FDA Submission - IND	**Protocol Amendment. New Investigators.S-081 Keogh, Noordegraaf, Jennings, Murali, Schilz, Campos, Chatkin, Arakaki, Cardozo, Meyer, Kopisa, Hassoun, Feldman. S-081**	**S-081**	64,915
1	Regulatory	US	**6/30/2005**	Book 51	FDA Submission - IND	**Protocol Amendment. Annual Report. S-080**	**S-080**	64,915
1	Regulatory	US	**6/20/2005**	Book 51	FDA Submission - IND	**Protocol Amendment: New Investigators. Badesch, Foley, McGoon, Hassoun, Oudiz. Other: Revisions to FDA Form 1572. S-079**	**S-079**	64,915
1	Regulatory	US	**5/24/2005**	Book 51	FDA Submission - IND	**General Correspondence: Converting ARIES-2 Study Sites to ARIES-1. S-078**	**S-078**	64,915
1	Regulatory	US	**5/23/2005**	Book 51	FDA Submission - IND	**Protocol Amendment: New Investigators. Baratz, Barst, Fairman, Garcia, Mandel, Oudiz, Test. S-077**	**S-077**	64,915
1	Regulatory	US	**5/6/2005**	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/M.Robb. Subject: Follow-up on requirement for food effects study.	**2005-05-06_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915

1	Regulatory	US	**5/3/2005**	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/M.Robb. Subject: Clarify message from Dr. Velazquez.	**2005-05-03_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915
1	Regulatory	US	**5/2/2005**	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/L.Velazquez. Subject: Protocol AMB-222.	**2005-05-02_64915_CORR_PHONE_LWEISSBERGER_LVELAZQUEZ.pdf**	64,915
1	Regulatory	US	**4/29/2005**	Book 51	FDA Correspondence - Email	Email/M.Robb/L.Weissberger - 2-Year Rat and Mouse Bioassays.	**2005-04-29_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**4/27/2005**	Book 51	FDA Submission - IND	**Protocol Amendment: New Investigators. S-076 Kilinger, Hurewitz, Feldman, Arfaei, Nikolaevich. S-076**	**S-076**	64,915
1	Regulatory	US	**4/25/2005**	Book 51	FDA Correspondence - Phone call	Phone call. L.Weissberger/T.Link. FDA Response to our proposal for carcinogenicity studies.	**2005-04-25_64915_CORR_PHONE_LWEISSBERGER_WLINK.pdf**	64,915
1	Regulatory	US	**4/22/2005**	Book 51	FDA Correspondence - Phone call	Call to discuss 2-yr. Carcinogenicity studies.	**2005-04-22_64915_CORR_PHONE_LWEISS**	64,915
1	Regulatory	US	**4/12/2005**	Book 51	FDA Submission - IND	**Protocol Amendment: Change in Protocol. S-075**	**S-075**	64,915
1	Regulatory	US	**4/5/2005**	Book 53-55	FDA Submission - IND	**Vol. 1 - 3 -Response to FDA Request for Information. S-074**	**S-074**	64,915
1	Regulatory	US	**4/1/2005**	Book 51	FDA Correspondence - Email	Email/M.Robb/L.Weissberger - Response to FDA Request for Information	**2005-04-01_64915_CORR_EMAIL_LTANNER_MROBB.pdf**	64,915
1	Regulatory	US	**3/31/2005**	Book 50	FDA Submission - IND	**Protocol Amendment - L. Weissberger. New Investigator, Test, Noordegraaf, Kovalenko, Zagolin, Revisions to FDA Forms 1572. S-073**	**S-073**	64,915
		US	**3/28/2005**	Book 50	FDA Correspondence - Fax	Response to a request from FDA, and follow-up	**2005-03-28_64915_CORR_FAX_JFLIARD_NBEASLEY.pdf**	64,915
1	Regulatory	US	**3/24/2005**	Book 50	FDA Submission - IND	**Follow-up to a written Report. S-072**	**S-072**	64,915
1	Regulatory	US	**3/16/2005**	Book 50	FDA Correspondence - Letter	Stockbridge, N., Letter: Response to S 068 - Protocol Submission	**2005-03-16_64915_CORR_LETTER_MROBB_LWEISSBERGER.pdf**	64,915

1	Regulatory	US	**3/9/2005**	Book 50	FDA Submission - IND	**L.Weissberger. Information Amendment. Pharmacology/Toxicology 2 year Rat and Mouse Carcinogenicity Studies. S-071**	**S-071**	64,915
1	Regulatory	US	**3/4/2005**	Book 50	FDA Submission - IND	**L. Weissberger. Protocol Amendment: New Investigators, Hassoun, Tereshchenko, Chakinala. S-070**	**S-070**	64,915
1	Regulatory	US	**2/18/2005**	Book 50	FDA Submission - IND	**L. Weissberger. General Correspondence. S-069**	**S-069**	64,915
1	Regulatory	US	**2/16/2005**	Book 50	FDA Correspondence - Phone call	FDA Contact Report - Telephone. M.Robb/L.Weissberger. Subject: Existing "Food Effect" Study.	**2005-02-16_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915
1	Regulatory	US	**2/15/2005**	Book 50	FDA Submission - IND	**L.Weissberger. New Protocol: AMB-222. S-068**	**S-068**	64,915
1	Regulatory	US	**2/4/2005**	Book 50	FDA Submission - IND	**L.Weissberger. Protocol Amendment New Investigators, Colque, Noordegraaf, Chazova (AMB-321, AMB-320/321-E) S-067**	**S-067**	64,915
1	Regulatory	US	1/9/2005	Book 50	FDA Submission - IND	L.Weissberger. Protocol Amendment. New Investigators (AMB-320, AMB-321, AMB-320/321-E) S-066	S-066	64,915
1	Regulatory	US	**12/22/2004**	Book 50	FDA Submission - IND	**L.Weissberger. Protocol Amendment: New Investigators, Taichman, Hurewitz, Gene, Kremer, Abrahamovych (AMB-320, AMB-321, AMB-320/321-E) S-065**	**S-065**	64,915
1	Regulatory	US	**12/17/2004**	Book 50	FDA Correspondence - Phone call	FDA Contact Report - Telephone. L.Weissberger/W.Link. Subject: Executive CAC decision about lowering dose(s) for 2 year rat and mouse bioassays.	**2004-12-17_64915_CORR_PHONE_WEISSBERGER_LINK.pdf**	64,915
1	Regulatory	US	**12/7/2004**	Book 50	FDA Submission - IND	**L.Weissberger-Information Amendment-Pharmacology/Toxicology. 2-year Rat and Mouse Carcinogenicity. S-064**	**S-064**	64,915

1	Regulatory	US	**11/12/2004**	Book 50	FDA Submission - IND	**L. Weissberger - Protocol Amendment: New Investigators: Kramer, M.R., Barst, R.J., Lawrence, E.C., Park, M.H., Schilz, R.J. (AMB-321, AMB-320/321-E) S-063**	**S-063**	64,915
1	Regulatory	US	**10/29/2004**	Book 49	FDA Submission - IND	**L. Weissberger - Protocol Amendment: New Investigators: Langleben, D., Carlson,R., Diez,F., Porcile,R., Ubaldini,J.E., Vico, M.L., Tereschenko,S., Semernin,E.N. (AMB-320, AMB-321, AMB-320/321-E) S-062**	**S-062**	64,915
1	Regulatory	US	**10/26/2004**	Book 49	FDA Correspondence - Fax	FDA Correspondence - Fax - Meeting Minutes 10/13/04.	**2004-10-26_64915_CORR_FAX_MTG_MINS_2004-10-13.pdf**	64,915
1	Regulatory	US	**10/22/2004**	Book 49	FDA Submission - IND	**L. Weissberger - Protocol Amendment-New Principal Investigators: Martinez,J.G., Vazquea,J., Chazova,Irina.Y., Kostenko, M.A., Czuriga,I., Landzberg, M.J., (AMB-320, AMB-321, AMB-320/321-E) S-061**	**S-061**	64,915
1	Regulatory	US	**10/5/2004**	Book 49	FDA Submission - IND	**L. Weissberger – Protocol Amendment. New Investigators. M. Amuchastegui,G. Bortman, E. Perna, K. Karlocai, O. Abrahamovysch, G.Dzyak, N. Kopitsa, V. Kovalenko, S. Polyvoda, F. Kleber, P. Podolec, A. Torbicki, V. McLaughlin, A. Towlar (AMB-320, AMB-321, AMB-320/321-E) S-060**	**S-060**	64,915
1	Regulatory	US	**9/27/2004**	Book 49	FDA Submission - IND	**Lynn Weissberger - Type C Meeting Information Package. S-059**	**S-059**	64,915

1	Regulatory	US	**9/7/2004**	Book 48	FDA Submission - IND	**Lynne Weissberger - Protocol Amendment. New Investigators. R. Sulica, I. Czuriga, P. Podolec, A. Torbicki, I. Ben-Dov, R.P. Allen, R.J. Oudiz (AMB-320, AMB-321, AMB-320/321-E) S-058**	**S-058**	64,915
1	Regulatory	US	**8/31/2004**	Book 48	FDA Submission - IND	**Lynne Weissberger - Annual Report 07-03-2003 through 07-02-2004. S-057**	**S-057**	64,915
1	Regulatory	US	**8/27/2004**	Book 48	FDA Submission - IND	**Protocol Amendment - L. Weissberger - Initial Written Report. 15-Day Safety Alert Report. (AMB-320/321-E) S-056**	**S-056**	64,915
1	Regulatory	US	**8/11/2004**	Book 48	FDA Correspondence - Fax	Fax from R. Fortney to L. Weissberger. Subject: Meeting confirmation with FDA for October 13, 2004.	**2004-08-11_64915_CORR_FAX_RFORTNEY_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	**8/10/2004**	Book 48	FDA Submission - IND	**L.Weissberger-Protocol Amendment New Investigators. R.Barst, M.Lamdzberg, M.A.G.Sanchez, J.A.Barbera, D.Badesch, R.Foley (AMB-320, AMB-320/321-E) S-055**	**S-055**	64,915
1	Regulatory	US	**8/9/2004**	Book 48	FDA Submission - IND	**L. Weissberger - Type C Meeting Request to discuss proposed changes to the ambrisentan program. S-054**	**S-054**	64,915
1	Regulatory	US	**7/20/2004**	Book 48	FDA Correspondence - Phone call	FDA Contact Report - Call to Alisea Sermon. Subject: Schedule Type C Meeting.	**2004-07-20_64915_CORR_PHONE_LWEISSBERGER_ASERMON.pdf**	64,915
1	Regulatory	US	**7/21/2004**	Book 48	FDA Correspondence - Email	FDA Contact Report - Email to A. Sermon. Subject: Meeting Request with the Division of Cardio-Renal drug Products.	**2004-07-21_64915_CORR_EMAIL_LWEISSBERGER_ASERMON.pdf**	64,915
1	Regulatory	US	**7/16/2004**	Book 47	FDA Correspondence - Phone call	FDA Contact Report - Call to M. Robb. Subject: Type C Meeting Request.	**2004-07-16_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915

1	Regulatory	US	**7/15/2004**	Book 47	FDA Correspondence - Email	FDA Contact Report - Email to M. Robb. Subject: Ambrisentan, Type C Meeting Request.	**2004-07-15_64915_CORR_EMAIL_LWEISSBERGER_MROBB.pdf**	64,915
1	Regulatory	US	**7/14/2004**	Book 47	FDA Submission - IND	**L. Weissberger- Protocol Amendment- New Investigators- A. Frost, P. Galvez, H. Donoso, M. Delcroix, G. Simonneau, J. Behr, R. Fairman, A. Frost (AMB-320, AMB-321, AMB-320/321-E) S-053**	**S-053**	64,915
1	Regulatory	US	**7/7/2004**	Book 47	FDA Submission - IND	**L. Weissberger- Protocol Amendment- New Investigators- D. Baratz, J. Edelman, N. Hill, I. Robbins, M. Robbins, S. Shapiro, S. Bhorade (AMB-320/321-E) S-052**	**S-052**	64,915
1	Regulatory	US	**6/23/2004**	Book 47	FDA Submission - IND	**L. Weissberger-Protocol Amendment- New Investigators – A. Waxman, P. Corris, A. Peacock, J. Pepke-Zaba, J. Gossage, J. Klinger, K. Mubarak, S. Murali (AMB-320, AMB-321, AMB-320/321-E) S-051**	**S-051**	64,915
1	Regulatory	US	**5/27/2004**	Book 47	FDA Correspondence - Letter	FDA Contact Report -AMB Orphan Drug Application - Amendment - Reference Number: 04-1836	**2004-05-27_ODA_US_AMENDMENT.pdf**	64,915
1	Regulatory	US	**5/7/2004**	Book 47	FDA Submission - IND	**L. Weissberger- Protocol Amendment: New Investigators R. Allen, S. Murali, R. Oudiz, J. Wirth, J. Behr, J. Albert Barbera, C. Black, R. Channick, M. McGoon, F. Torres (AMB-320, AMB-321, AMB-320/321-E) S-050**	**S-050**	64,915
1	Regulatory	US	**5/6/2004**	Book 46	FDA Submission - IND	**L. Weissberger- Protocol Amendment: Change in Protocols: 320, 321, 320/321-E. S-049**	**S-049**	64,915

1	Regulatory	US	**5/3/2004**	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Call to Melissa Robb. Subject: To discuss darusentan submission & PK program for ambrisentan.	**2004-05-03_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915
1	Regulatory	US	**4/28/2004**	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Call to Brad Glasscock, Tan Nguyen. Subject: To clarify request for information from Brad Glasscock.	**2004-04-28_64915_CORR_PHONE_LWEISSBERGER_GLASSCOCK.pdf**	64,915
1	Regulatory	US	**4/22/2004**	Book 46	FDA Correspondence - Email	FDA Contact Report - Email. L.Weissberger/P.Marroum. Email with attached word document - Feedback on Proposed Changes to AMB-320/321-E.	**2004-04-22_64915_CORR_EMAIL_LWEISSBERGER_PMARROUM.pdf**	64,915
1	Regulatory	US	**4/21/2004**	Book 46	FDA Correspondence - Phone call	FDA Contact Report - Dr. Glasscock called to inquire as to the status of the requested amendment.	**2004-04-21_64915_CORR_PHONE_BGLASCOCK_LWEISSBERGER.pdf**	64,915
1	Regulatory	US	**4/12/2004**	Book 46	FDA Submission - IND	**Protocol Amendment - L. Weissberger- New Investigators J. Edelman, J. Mandel, M. Park, R. Schilz, H. Olschewski (AMB-320, AMB-321, AMB-320/321-E) S-048**	**S-048**	64,915
1	Regulatory	US	**4/8/2004**	Book 46	FDA Correspondence - Phone call	FDA Contact Report- Call to Jeffrey Fritsch to inquire the status of application – J. Fritsch was out of office and Mary Grice answered questions.	**2004-04-08_64915_CORR_PHONE_LWEISSBERGER_BGLASSCOCK.pdf**	64,915
1	Regulatory	US	**4/7/2004**	Book 46	FDA Correspondence - Phone call	FDA Contact Report- Comments on proposed changes to extension protocol - pop: K and PK sub study.	**2004-04-07_64915_CORR_PHONE_LWEISSBERGER_MROBB.pdf**	64,915
1	Regulatory	US	**3/26/2004**	Book 45	FDA Submission - IND	**Protocol Amendment - L. Weissberger- New Investigators- N. Hill, C. Jennings, M. McGoon, D. Zwicke, S. Maruti Bhorade (AMB-320, AMB-321, AMB-320/321-E) S-047**	**S-047**	64,915
1	Regulatory	US	**3/25/2004**	Book 45	FDA Submission - IND	**L. Weissberger-Type C Meeting Request. S-046**	**S-046**	64,915
1	Regulatory	US	**3/17/2004**	Book 45	FDA Submission - IND	**L. Weissberger-Pharmacology/Toxicology 2-Year Rat and Mouse Final Protocols. S-045**	**S-045**	64,915

1	Regulatory	US	**3/5/2004**	Book 45	FDA Submission - IND	**Protocol Amendment - L. Weissberger- New Investigators- D. Badesch, R. Foley, E. Lawrence, I. Robbins, S. Shapiro (AMB-320) S-044**	**S-044**	64,915
1	Regulatory	US	**2/27/2004**	Book 44	FDA Submission - IND	**Protocol Amendment - L. Weissberger- New Investigators- R. Channick, K. Mubarak, F. Torres, R. Naeija, N. Galie, A Keogh (AMB-320, AMB-321, AMB-320/321-E) S-043**	**S-043**	64,915
		US	**2/24/2004**	Book 44	FDA Correspondence - Fax	Response to Carcinogenicity Protocol Assessment Request - Final CAC Report.	**2004-02-24_64915_CORR_FAX_SEIFRIED_WALDO.pdf**	64,915
1	Regulatory	US	**2/24/2004**	Book 44	FDA Correspondence - Letter	J. Fritsch- Acknowledge receipt of application for orphan designation submitted.	**2004-02-24_ODA_US_CORR_LETTER_ASSIGN_ODA_NUMBER.pdf**	64,915
1	Regulatory	UK	**2/20/2004**	Book 44	Foreign Correspondence - MHRA	Clinical Trial Application UK - MHRA-Exemption from licenses.	**2004-02-20_64915_MHRA_CORR_LETTER.pdf**	64,915
1	Regulatory	US	**2/16/2004**	Book 44	FDA Submission - IND	**Protocol Amendment - L. Weissberger- New Investigators- J. Gossage, M. Delcroix, G. Simonneau, F. Xaver Kleber, I. Ben-Dov, and P. Engel (AMB-320, AMB-321, AMB-320/321-E) S-042**	**S-042**	64,915
1	Regulatory	US	**2/13/2004**	Book 44	FDA Submission - IND	**L. Weissberger-Information Amendment- Updated IB. S-041**	**S-041**	64,915
1	Regulatory	US	**1/30/2004**	Book 44	FDA Submission - IND	**L. Weissberger-Change in US Agent from Quintiles, Inc. to Myogen, Inc. S-040**	**S-040**	64,915
1	Regulatory	US	**1/28/2004**	Book 44	FDA Correspondence - Fax	Fax - Response to Carcinogenicity Protocol Assessment Request - Final CAC Report.	**2004-01-28_64915_CORR_FAX_FDA.pdf**	64,915
1	Regulatory	US	**1/16/2004**	Book 44	FDA Correspondence - Fax	Z. McDonald- Receipt of request - Serial No. 036 for a special carcinogenicity protocol assessment.	**2004-01-16_64915_CORR_FAX_FDA.pdf**	64,915

1	Regulatory	US	**1/15/2004**	Book 44	FDA Submission - IND	**Protocol Amendment - New Investigators-R. Fairman, M. Robbins, H. Garcia (AMB-320, AMB-320/321-E) S-039**	**S-039**	64,915
1	Regulatory	US	**1/14/2004**	Book 44	FDA Correspondence - Email	Email Communication regarding special assessment for 2-year mouse carcinogenicity protocol.	**2004-01-14_64915_CORR_EMAIL_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**1/12/2004**	Book 44	FDA Submission - IND	**Courtesy copy of Orphan Drug Application (Cover Letter) S-038**	**S-038**	64,915
1	Regulatory	US	**1/6/2004**	Book 44	FDA Submission - IND	**Protocol Amendment - New Investigators- Keogh, Baratz, Engel, Garcia, Klinger (AMB-320-E) S-037**	**S-037**	64,915
1	Regulatory	US	**1/5/2004**	Book 44	FDA Correspondence - Letter	Letter from - M. Gerber to Dr. Haffner about transfer of responsibility as US Agent and Authorized Representative effective Dec. 12, 2003, quintiles, Inc. assumes the responsibility from Myogen, Inc. as the US Agent to interact with the office of Orphan Products Development	**2004-01-05_64915_CORR_LETTER_HAFNER_WALDO.pdf**	64,915
1	Regulatory	US	1/5/2004	Book 44	FDA Correspondence - Letter	Letter from C. Waldo to Dr. Haffner regarding application for Orphan Drug designation.	2004-01-05A 64915 CORR LETTER HAFNER WALDO.pdf	64,915
1	Regulatory	US	**12/18/2003**	Book 43	FDA Submission - IND	**Request for Special Protocol Assessment 2-Year Mouse Carcinogenicity Protocol. S-036**	**S-036**	64,915
1	Regulatory	US	**12/2/2003**	Book 43	FDA Submission - IND	**Change in Protocol: 220-E. S-035**	**S-035**	64,915
1	Regulatory	US	**11/24/2003**	Book 43	FDA Correspondence - Fax	FDA Contact Report. Fax. Subject: Response to Carcinogenicity Protocol Assessment Request - Final CAC Report - IND 64,915	**2003-11-24_64915_CORR_FAX_SEIFRIED_WALDO.pdf**	64,915
1	Regulatory	US	**10/20/2003**	Book 43	FDA Correspondence - Letter	FDA Contact Report-Z. McDonald-Acknowledgement of receipt from Oct. 13, 2003, request for a special carcinogenicity protocol assessment.	**2003-10-20_64915_CORR_LETTER_ZMCDONALD_MGERBER.pdf**	64,915
1	Regulatory	US	**10/13/2003**	Book 43	FDA Submission - IND	**Request for special protocol assessment 2-Year Rat Carcinogenicity Protocol. S-034**	**S-034**	64,915

1	Regulatory	US	**10/9/2003**	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Response to questions.	**2003-10-09_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**10/8/2003**	Book 42	FDA Correspondence - Email	C. Waldo-Response to Carcinogenicity Protocol Assessment Request.	**2003-10-08_64915_CORR_EMAIL_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**10/8/2003**	Book 42	FDA Submission - IND	**New Phase III Protocols: 320, 321, 320/321-E Response Requested. S-033**	**S-033**	64,915
1	Regulatory	US	**10/7/2003**	Book 42	FDA Correspondence - Email	FDA Contact Report- Email - Phase III Protocols. C. Waldo.	**2003-10-07_64915_CORR_EMAIL_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**10/7/2003**	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Regarding request for feedback.	**2003-10-07_64915_CORR_PHONE_WALDO_ROBB.pdf**	64,915
1	Regulatory	US	**10/7/2003**	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Phone call - Left v-mail regarding request for feedback.	**2003-10-07A_64915_CORR_PHONE_ROBB_WALDO.pdf**	64,915
1	Regulatory	US	**9/9/2003**	Book 42	FDA Correspondence - Fax	FDA Correspondence - Fax - 8/27/03 Meeting Minutes.	**2003-09-09_64915_CORR_FAX_ROBB_WALDO.pdf**	64,915
1	Regulatory	US	**9/9/2003**	Book 42	FDA Correspondence - Phone call	FDA Contact Report- Confirm receipt of fax containing the meeting minutes from the 8/27/2003 meeting with the division.	**2003-09-09_64915_CORR_PHONE_ROBB_WALDO.pdf**	64,915
1	Regulatory	US	**9/9/2003**	Book 42	FDA Submission - IND	**Protocol Amendment: New investigators: D. Badesch, M. McGoon, S. Rich, M . Landzberg, R. Barst (AMB-220-E) S-032**	**S-032**	64,915
1	Regulatory	US	**9/4/2003**	Book 42	FDA Correspondence - Phone call	FDA Contact Report-Special Protocol Assessment.	**2003-09-04_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**9/3/2003**	Book 42	FDA Submission - IND	**IND Annual Report. S-031**	**S-031**	64,915
1	Regulatory	US	**8/27/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Verify FDA meeting attendees.	**2003-08-27_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**8/27/2003**	Book 41	FDA Correspondence - Meeting	Meeting Minutes from - August 27, 2003 meeting with FDA.	**2003-08-27_64915_CORR_MEETING_CWALDO_MROBB.pdf**	64,915

1	Regulatory	US	**8/22/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- End of Phase II Meeting.	**2003-08-22_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**8/8/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Copies for August 27 Meeting.	**2003-08-08_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**8/8/2003**	Book 41	FDA Correspondence - Letter	FDA Correspondence - Letter - 4 Additional copies of the info. Package for 8/27/03 meeting.	**2003-08-08_64915_CORR_LETTER_INFO_PKG_COPIES.pdf**	64,915
1	Regulatory	US	**8/7/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- Confirm FDA receipt of Briefing Document for August 27 Meeting.	**2003-08-07_64915_CORR_PHONE_CWALDO_MROBB.pdf**	64,915
1	Regulatory	US	**8/5/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report-End of Phase II briefing package.	**2003-08-05_64915_CORR_PHONE_MROBB_CWALDO.pdf**	64,915
1	Regulatory	US	**8/5/2003**	Book 41	FDA Submission - IND	**Information Package for August 27, 2003 Meeting. S-030**	**S-030**	64,915
1	Regulatory	US	**7/25/2003**	Book 41	FDA Submission - IND	**Protocol Amendment: New Investigators: Teresa De Marco (AMB-220-E) S-029**	**S-029**	64,915
1	Regulatory	US	**7/10/2003**	Book 41	FDA Submission - IND	**FDA - General Correspondence - Contact Information. S-028**	**S-028**	64,915
1	Regulatory	US	**7/8/2003**	Book 41	FDA Correspondence - Fax	FDA Contact Report -Confirmation of Meeting g: August 27, 2003	**2003-07-08_64915_CORR_FAX_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**7/7/2003**	Book 41	FDA Submission - IND	**Protocol Amendment: New Investigators-I. Robbins, S. Shapiro, AMB-220-E. S-027**	**S-027**	64,915
1	Regulatory	US	**7/2/2003**	Book 41	FDA Submission - IND	**Meeting Request: Type B. Request for Re-Scheduling. S-026**	**S-026**	64,915
1	Regulatory	US	**7/2/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- M. Robb requested that we resubmit the request to reschedule the end of phase II meeting for IND 64,915	**2003-07-02_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**6/26/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report-R. Fortney checked on request to re-schedule the end-of Phase II meeting with Melissa Robb.	**2003-06-26_64915_CORR_PHONE_RFORTNEY_MENLOW.pdf**	64,915

		US	**6/24/2003**	Book 41	FDA Submission - IND	**IND - Meeting Request - Type B Request for Re-Scheduling. S-025**	**S-025**	64,915
1	Regulatory	US	**6/23/2003**	Book 41	FDA Correspondence - Phone call	FDA Contact Report- M.Robb requested that the end of Phase II meeting originally scheduled for July 11, 2003 be re-scheduled.	**2003-06-23_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**6/13/2003**	Book 41	FDA Submission - IND	**Protocol Amendment: New Investigators and Revision to FDA form 1572 (AMB-220-E) S-024**	**S-024**	64,915
1	Regulatory	US	**5/23/2003**	Book 40	FDA Correspondence - Fax	FDA Contact Report-Fax - Confirmation of 7/11/03.	**2003-05-23_64915_CORR_FAX_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**5/23/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report-M. Robb called Project Manager to confirm receipt of fax	**2003-05-23_64915_CORR_PHONE_ATANNER_MROBB.pdf**	64,915
1	Regulatory	US	**5/15/2003**	Book 40	FDA Correspondence - Fax	FDA Correspondence - Fax - Formal meeting request for an End of Phase II meeting.	**2003-05-15_64915_CORR_FAX_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**5/15/2003**	Book 40	FDA Submission - IND	**Meeting Request : Type B. S-023**	**S-023**	64,915
1	Regulatory	US	**5/6/2003**	Book 40	FDA Submission - IND	**Protocol Amendment- New Investigators. S-022**	**S-022**	64,915
1	Regulatory	US	**5/2/2003**	Book 40	FDA Submission - IND	**IND Safety Report – Follow-up IND Safety Report Mfg. Rpt. No. 29404 (Follow-up 1) S-021**	**S-021**	64,915
1	Regulatory	US	**4/22/2003**	Book 40	FDA Submission - IND	**General Correspondence – Transfer of Regulatory Obligations. S-020**	**S-020**	64,915
1	Regulatory	US	**4/1/2003**	Book 40	FDA Submission - IND	**General Correspondence – Duration of Chronic Toxicity Study. M. Enlow/D. Throckmorton. S-019**	**S-019**	64,915
1	Regulatory	US	**3/20/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Inquire about letter of intent for submission of Special Carcinogenicity Protocol submission.	**2003-03-20_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915

1	Regulatory	US	**3/19/2003**	Book 40	FDA Submission - IND	**General Correspondence – Copy of letter to investigators regarding two deaths (unrelated) and consent form changes. M.Enlow/D.Throckmorton. S-018**	**S-018**	64,915
1	Regulatory	US	**3/11/2003**	Book 40	FDA Submission - IND	**General Correspondence – Copy of Investigator Notification of IND Safety Report for elevated Liver Function Tests. M.Enlow/D.Throckmorton. S-017**	**S-017**	64,915
1	Regulatory	US	**3/10/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Express concern that report of elevated LFTs to greater than 8 times upper limit of normal was not initially considered a SAE and suggest the sponsors remind investigators of potential for hepatotoxicity and need for SAE reporting of such event. JPelayo, MD/M.Enlow.	**2003-03-10_64915_CORR_PHONE_JPELAYO_MENLOW.pdf**	64,915
1	Regulatory	US	**3/7/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Project Manager communicates FDA decision on extension protocol AMB-220-E. L.Tanner/M.Robb.	**2003-03-07_64915_CORR_PHONE_MROBB_ATANNER.pdf**	64,915
1	Regulatory	US	**3/5/2003**	Book 40	FDA Submission - IND	**IND 15-Day ADR Report. M. Enlow/FDA. S-016**	**S-016**	64,915
1	Regulatory	US	**3/5/2003**	Book 40	FDA Correspondence - Fax	FDA Correspondence - Fax - Fax of submission dated 3/5/03 S-016.	**2003-03-05_64915_CORR_FAX_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**2/28/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss case of increased liver function tests reported in study AMB-220.	**2003-02-28_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**2/27/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Check status of Division's review of extension Protocol, AMB-220-E. M. Enlow/M. Robb	**2003-02-27_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**2/11/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss Typo's of year submitted on Protocol AMB220-E.	**2003-02-11_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**2/7/2003**	Book 40	FDA Submission - IND	**Protocol Amendment: New Protocol AMB 220-E. S-015**	**S-015**	64,915

1	Regulatory	US	**2/5/2003**	Book 40	FDA Submission - IND	**Protocol Amendment: New Investigators –McGoon, Landzberg, Marco. S-014**	**S-014**	64,915
1	Regulatory	US	**1/27/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Inform sponsors the Division is still discussing internally the open-label extension study, protocol AMB-222, and timing relative to the non-rodent chronic toxicity study.	**2003-01-27_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**1/24/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Discuss open-label extension study, protocol AMB-222, and timing relative to non-rodent chronic toxicity study. M. Robb & M. Enlow	**2003-01-24_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**1/20/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report: Message left-update on feedback request for proposal to provide open-label treatment beyond 24 wks.	**2003-01-20_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**1/14/2003**	Book 40	FDA Submission - IND	**Response to FDA Request – submitting safety monitoring plans for 12-wk Open-label Extension Period for AMB 220 and draft safety monitoring plans for AMB 222. S-013**	**S-013**	64,915
1	Regulatory	US	**1/14/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Confirm 12-wk extension period in Protocol AMB-220 could proceed.	**2003-01-14_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**1/13/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report – FDA Project Manager called to request additional IND 64,915 information. M.Robb and A. Tanner	**2003-01-13_64915_CORR_PHONE_MROBB_ATANNER.pdf**	64,915
1	Regulatory	US	**1/13/2003**	Book 40	FDA Correspondence - Fax	FDA Contact Report – Fax - Response to FDA Request for additional information regarding IND 64,915.	**2003-01-13_64915_CORR_FAX_TANNER_MROBB.pdf**	64,915
1	Regulatory	US	**1/10/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Discuss causes of death in some animals in 26-wk rat toxicity study. M. Enlow & W. Link.	**64915_CORR_PHONE_MENLOW_M**	64,915
1	Regulatory	US	**1/10/2003**	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Inquire whether Melissa could provide update on Division's position on the explanation given for mortality in 26 wk rat toxicity study and moving into the extension phase of the clinical study.	**2003-01-10A_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915

1	Regulatory	US	1/9/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Clarify their internal mtg. to discuss 26-wk toxicity studies & open-label extensions to the clinical study.	**2003-01-09_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	1/9/2003	Book 40	FDA Submission - IND	**Protocol Amendment – New Investigators: AMB-220 Simonneau, France; McLaughlin, Robbins, & Shapiro, United States. S-012**	**S-012**	64,915
1	Regulatory	US	1/9/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Arrange time for phone conference to discuss questions about he 26-wk toxicity study. W. Link , M. Enlow.	**2003-01-09_64915_CORR_PHONE_MENLOW_WLINK.pdf**	64,915
1	Regulatory	US	1/8/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report - To clarify the date of their internal meeting to discuss the 26-week toxicity studies and the open-label extensions to the clinical study.	**2003-01-08_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	1/2/2003	Book 40	FDA Submission - IND	**General Correspondence – Rationale & Study Summary for additional long-term protocol. From Quintiles to Dr. Throckmorton. S-011**	**S-011**	64,915
1	Regulatory	US	1/2/2003	Book 40	FDA Correspondence - Phone call	FDA Contact Report – Informed Melissa Robb that faxed copy of submission w- Rationale & Study Summary for Protocol AMB-222 sent.	**2003-01-02_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	1/2/2003	Book 40	FDA Correspondence - Fax	FDA Contact Report – Fax - Copy of submission with rationale and study summary of S-011.	2003-01-02_64915_CORR_FAX_MENLOW_MROBB.pdf	64,915
1	Regulatory	US	12/30/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Follow-up regarding extension of treatment beyond 6 months.	**2002-12-30_64915_CORR_PHONE_ENLOW_ROBB.pdf**	64,915
1	Regulatory	US	12/24/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Follow-up regarding extension of treatment beyond 6 months.	**2002-12-24_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	12/23/2002	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Inquire about date of Division's Internal mtg. To discuss 26 wk toxicity studies and whether Division would consider clinical extension protocol for treatment beyond 6 months.	**2002-12-23_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915

1	Regulatory	US	**12/12/2002**	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Quintiles that the Division scheduled an internal mtg. In January 2003 to discuss 26 wk toxicology studies.	**2002-12-12_64915_CORR_PHONE_MROBB_MENLOW.pdf**	64,915
1	Regulatory	US	**12/11/2002**	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Melissa Robb, new FDA project mgr. That the 26 wk toxicity study submitted and receipt confirmed.	**2002-12-11_64915_CORR_PHONE_MENLOW_MROBB.pdf**	64,915
1	Regulatory	US	**12/10/2002**	Book 2	FDA Correspondence - Phone call	FDA Contact Report – Informed Zelda that 26 wk toxicology draft study report submitted. Zelda to provide name & phone # of new FDA project mgr for IND.	**2002-12-10_64915_CORR_PHONE_MENLOW_ZMCDONALD.pdf**	64,915
1	Regulatory	US	**12/9/2002**	Book 34-39	FDA Submission - IND	**Vol. 1 - 6 - Response to FDA Request for Information – 26 wk. Toxicity Studies (Draft Reports: Dog and Rat) S-010**	**S-010**	64,915
1	Regulatory	US	**11/8/2002**	Book 2	FDA Submission - IND	**Protocol Amendment - New Investigators – Olschewski, Schilz, Germany and United States (AMB-220) S-009**	**S-009**	64,915
1	Regulatory	US	**11/6/2002**	Book 2	FDA Submission - IND	**Information Amendment: Clinical. S-008**	**S-008**	64,915
1	Regulatory	US	**10/29/2002**	Book 1	FDA Submission - IND	**Response to FDA Request for Information – Chemistry, Manufacturing & Controls. S-007**	**S-007**	64,915
1	Regulatory	US	**10/18/2002**	Book 1	FDA Submission - IND	**New Investigators – Keogh, Naeije, Hoeper, Galie, Rubin, Frost, Zwicke, Australia, Belgium, Germany, Italy and United States (AMB-220) S-006**	**S-006**	64,915
1	Regulatory	US	**9/25/2002**	Book 1	FDA Submission - IND	**Protocol Amendment – New Investigators – DBadesch and Rdoyle (AMB-220) S-005**	**S-005**	64,915
1	Regulatory	US	**9/20/2002**	Book 1	FDA Correspondence - Letter	FDA Contact Report – FDA completed chemistry review of 7-17-2002 (S-002) submission & provided comments-requests. Dthrockmorton-JMFreytag-Myogen Menlow.	**2002-09-20_64915_CORR_LETTER_DTHROCKMORTON_WFREYTAG.pdf**	64,915
1	Regulatory	US	**9/10/2002**	Book 1	FDA Submission - IND	**Protocol Amendment – New Investigators US: ROudiz 004 (AMB-220) - S-004**	**S-004**	64,915

1	Regulatory	US	**8/30/2002**	Book 1	FDA Submission - IND	**Protocol Amendment – Submitted Amendment 1, dated 7-26-2002 for Protocol No. AMB-220 (No Suggestions) - S-003**	**S-003**	64,915
1	Regulatory	US	**7/31/2002**	Book 1	FDA Correspondence - Letter	FDA Contact Report – Letter from FDA with regard to Clinical Trials Data Bank, asking for review of protocol submitted with S-000 to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness.	**2002-07-31_64915_CORR_LETTER_JWOODCOCK_CKIRK.pdf**	64,915
1	Regulatory	US	**7/17/2002**	Book 33	FDA Submission - IND	**Information Amendment: Amendment to provide updated info for drug substance and drug product. (CHEMISTRY) - S-002**	**S-002**	64,915
1	Regulatory	US	**6/28/2002**	Book 1	FDA Submission - IND	**Information Amendment: Clinical Revised Informed Consent Form - S-001**	**S-001**	64,915
1	Regulatory	US	**6/28/2002**	Book 1	FDA Correspondence - Fax	FDA Contact Report – Inform Zelda a revised Informed Consent form for Protocol AMB-220 was being sent to her as requested by Dr. Stockbridge.	**2002-06-28_64915_CORR_FAX_MENLOW_ZMCDONALD.pdf**	
1	Regulatory	US	**6/28/2002**	Book 1	FDA Correspondence - Phone call	FDA Contact Report – Inform Zelda a revised Informed Consent form for Protocol AMB-220 was being sent to her as requested by Dr. Stockbridge.	**2002-06-28_64915_CORR_PHONE_MENLOW_ZMCDONALD.pdf**	64,915
1	Regulatory	US	**6/25/2002**	Book 1	FDA Correspondence - Phone call	FDA Contact Report – Request Chg to Informed Consent document & discuss Pharm-Tox required for supporting open-label extension study.	**2002-06-25_64915_CORR_PHONE_NSTOCKBRIDGE_MENLOW.pdf**	64,915
1	Regulatory	US	**6/25/2002**	Book 1	FDA Correspondence - Phone call	FDA Contact Report – Called Monica Cooper to discuss questions about stability data for the drug product.	**2002-06-25_64915_CORR_PHONE_MENLOW_MCOOPER.pdf**	64,915
1	Regulatory	US	**6/24/2002**	Book 1	FDA Correspondence - Phone call	FDA Contact Report – Monica Cooper call Marguerite -asked a few questions about the stability data for the drug product.	**2002-06-24_64915_CORR_PHONE_MCOOPER_MENLOW.pdf**	64,915
1	Regulatory	US	**6/10/2002**	Book 1	FDA Correspondence - Letter	FDA Correspondence - Letter - Acknowledgement of receipt of IND Application submitted.	**2002-06-10_64915_CORR_LETTER_ZMCDONALD_WFREYTAG.pdf**	

1	Regulatory	US	6/6/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report – To check-confirm receipt by Zelda of IND Submission.	2002-06-06_64915_CORR_PHONE_ZMCDONALD_MENLOW.pdf	64,915
1	Regulatory	US	6/3/2002	Book 1	FDA Correspondence - Phone call	FDA Contact Report – Inform Zelda BSF 208075 IND for PAH was shipped to FDA on June 3, 2002.	2002-06-03_64915_CORR_PHONE_MENLOW_ZMCDONALD.pdf	64,915
1	Regulatory	US	6/3/2002	Book 1-22	FDA Submission - IND	Vol. 1 - 30 - Initial Submission BSF 208075 IND Pulmocyte Aerosol Hydrofluoroalkane Propelled 4 MG 220 S-000	S-000	64,915

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Ambrisentan: Pulmonary Arterial Hypertension - NDA 22-081 - CORRESPONDENCE

LINK TO NDA AMENDMENTS

Product	Department	Country	Document Date	Book Number	Document Type	Document Title	E-Copy	Keywords
1	Regulatory	US	7/20/2007	Temp 6	FDA Correspondence - Phone	H.Isokoski/D.Brum - phone call. Subject: Spanish translations of the RiskMAP tools. New reminder tools for LEAP. Correct address for waiver request for MedWatch forms for non-serious and labeled adverse events (Aes)	2007-07-20_22081_CORR_PHONE_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/20/2007	Temp 6	FDA Correspondence - Email	D.Brum - 7/20/2007 on foreign language translation.	2007-07-20_22081_CORR_EMAIL_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/16/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Postmarketing Study Commitment Correspondence and Patent Information. NDA 22-081	2007-07-16_22081_CORR_EMAIL_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/13/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Postmarketing Study Commitment Correspondence and Patent Information. NDA 22-081	2007-07-13_22081_CORR_EMAIL_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/11/2007	Temp 6	FDA Correspondence - Phone	D.Brum/H.Isokoski - Letairis RiskMAP. To update the Division on the status of the submission and seek their advice on correct process.	2007-07-11_22081_CORR_PHONE_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/11/2007	Temp 6	FDA Correspondence - Email	D.Brum/H.Isokoski - Letairis RiskMAP.	2007-07-11_22081_CORR_EMAIL_HISOKOSKI_DBRUM.pdf	22-081
1	Regulatory	US	7/9/2007	Temp 6	FDA Correspondence - Phone	T.Marshall/T.Bouie - Phone calls on June21, June 29 and July 9, 2007. Subject: Post-Approval Supplement for Change to RPM in Dissolution Method. NDA 22-081	2007-07-09_22081_CORR_PHONE_TBOUIE_TMARSHALL.pdf	22-081

1	Regulatory	US	7/9/2007	Temp 6	FDA Correspondence - Email	T.Marshall/T.Bouie - Teleconference (July 10) information with the list of attendees from Gilead and FDA attendees. NDA 22-081 for Letairis Tablets-Proposal for CBE-30 Post Approval Supplement-Increase in Dissolution Method Paddle Speed.	2007-07-09_22081_CORR_EMAIL_TMARSHALL_TBOUIE.pdf	22-081
1	Regulatory	US	7/6/2007	Temp 6	FDA Correspondence - Email	L.Tanner/D.Brum - Notification of Last Day at Gilead.	2007-07-06_22081_CORR_EMAIL_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	7/3/2007	Temp 6	FDA Correspondence - Email	L.Tanner/D.Brum - Respond from D.Brum to the questions regarding the Revising RiskMAP and Materials to Reflect "Prescriber"	2007-07-03_22081_CORR_EMAIL_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	7/2/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Subject: Pediatric Plan. Revisions to RiskMAP and educational materials.	2007-07-02_22081_CORR_PHONE_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	7/2/2007	Temp 6	FDA Correspondence - Email	L.Tanner/D.Brum - Proposed Plan for Revising RiskMAP and Materials to Reflect "Prescriber"	2007-07-02_22081_CORR_EMAIL_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/22/2007	Temp 6	FDA Correspondence - Email	T.Marshall/T.Bouie - Proposal for CBE-30 Post Approval Supplement_ Increase in Dissolution Method Paddle Speed. NDA 22-081	2007-06-22_22081_CORR_EMAIL_TBOUIE_TMARSHALL.pdf	22-081
1	Regulatory	US	6/21/2007	Temp 6	FDA Correspondence - Phone	T.Marshall/S.Goldie - Post-Approval Supplement for Change to RPM in Dissolution Method. NDA 22-081	2007-06-21_22081_CORR_PHONE_TMARSHALL_SGOLDIE.pdf	22-081
1	Regulatory	US	6/19/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Subject: Administrative process for post-approval submissions of PI to the NDA	2007-06-19_22081_CORR_PHONE_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/15/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Subject: Final processes for approval. NDA 22-081	2007-06-15_22081_CORR_PHONE_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/15/2007	Temp 6	FDA Correspondence - Letter	R.Temple/L.Tanner - The NDA 22-081 - Letairis, Approval Letter from FDA. PI attached.	\2007-06-15_22081_CORR_LETTER_RTEMPLE_LTANNER.pdf	22-081
1	Regulatory	US	6/15/2007	Temp 6	Internal Correspondence - Labeling Approval	ABS - GS22-081-000: LETAIRIS (ambrisentan) 5 and 10 mg tablets - RAAN CMC - Approved in the US on June 15, 2007	2007-06-15_22081_CORR_RAAN_NOTIFICATION.pdf	22-081

1	Regulatory	US	**6/14/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum, T.Marciniak, J.Hung - Resolve remaining issues with PI.	**2007-06-14_22081_CORR_PHONE_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**6/13/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Issues with opening files during Label Negotiation. Cancellation of teleconference between Gilead and FDA.	**2007-06-13_22081_CORR_PHONE_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**6/12/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum, J.Weaver, S.Berkman - Remaining issues with the RiskMAP	**2007-06-12_22081_CORR_PHONE_LTANNER_DBRUM_2.pdf**	22-081
1	Regulatory	US	**6/12/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum - Final inspection report for Site #207 (Nazzareno Galie) Italy. Next steps for submitting Gilead comments for PI. Teleconference with FDA on Wednesday, 13 June 2007. Teleconference to discuss cyclosporine contraindication.	**2007-06-12_22081_CORR_PHONE_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**6/11/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/T.Marciniak - Feedback regarding FDA comments to PI.	**2007-06-11_22081_CORR_PHONE_LTANNER_TMARCINIAK.pdf**	22-081
1	Regulatory	US	**6/11/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/R.Fortney - The phone calls (6/8/2007 & 6-11-2007) to proactively schedule teleconference to resolve any remaining NDA issues, particularly with the PI.	**2007-06-11_22081_CORR_PHONE_LTANNER_RFORTNEY.pdf**	22-081
1	Regulatory	US	**6/11/2007**	Temp 6	FDA Correspondence - Email	T.Marshall/G.Scott - Attachment NDA 22-081 Amend 019. Summary of CMC Agreements Reached During June 8, 2007 CMC Teleconference	**2007-06-11_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf**	22-081
1	Regulatory	US	**6/11/2007**	Temp 6	FDA Correspondence - Email	T.Marshall/G.Scott - Update on Gilead's ABS NDA 22-081 Amend 019. Summary of CMC Agreements Reached During June 8, 2007 CMC Teleconference	**2007-06-11_22081_CORR_EMAIL_SGOLDIE_TMARSHALL_1.pdf**	22-081
1	Regulatory	US	**6/8/2007**	Temp 6	FDA Correspondence - Phone	L.Tanner/T.Marciniak - Feedback regarding FDA comments to PI.	**2007-06-08_22081_CORR_PHONE_LTANNER_TMARCINIAK.pdf**	22-081
1	Regulatory	US	**6/8/2007**	Temp 6	FDA Correspondence - Email	T.Marshall/G.Scott - T Con participants.	**2007-06-08_22081_CORR_EMAIL_SGOLDIE_TMARSHALL_1.pdf**	22-081

1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email	D.Brum/L.Tanner - Notifications about comments on PI.	2007-06-07_22081_CORR_EMAIL_LTANNER_DBRUM_2.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/D.Brum. The phone calls on 06/06/07 and 06/07/07. Process and Timing for Receiving FDA Comments to PI. Process for submitting revised RiskMAP and associated Materials.	2007-06-07_22081_CORR_PHONE_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email	L.Tanner/D.Brum. NDA 22-081: Tracleer Label	2007-06-07_22081_CORR_EMAIL_LTANNER_DBRUM_1.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Email	L.Tanner/D.Brum. NDA 22-081: Comments on Proposed RiskMAP	2007-06-07_22081_CORR_EMAIL_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/M.Gordon - Subject: Processes and Timing for Receiving FDA Comments to PI. Processes for submitting revised RiskMAP and associated Materials.	2007-06-07_22081_CORR_PHONE_LTANNER_DBRUM_2.pdf	22-081
1	Regulatory	US	6/7/2007	Temp 6	FDA Correspondence - Phone	L.Tanner/M.Gordon - The phone calls to confirm that CRF pages for subject 2050/248-001resent and that there are no further outstanding issues regarding input into the PI.	2007-06-07_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	6/6/2007	Book 5	FDA Correspondence - Email	M.Gordon/L.Tanner - &-day report; Subject 2050/248-001 (updated forms). The CRF's forms attached.	2007-06-06_22081_CORR_EMAIL_LTANNER_MGORDON_1.pdf	22-081
1	Regulatory	US	6/6/2007	Book 5	FDA Correspondence - Email	M.Gordon/L.Tanner - Message email from May 29, 2007 has been lacked.	2007-06-06_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	6/6/2007	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. NDA 22-081: Reformatted MedGuide for LETAIRIS™(ambrisentan)	2007-06-06_22081_CORR_EMAIL_LTANNER_DBRUM.pdf	22-081
1	Regulatory	US	6/5/2007	Book 5	FDA Correspondence - Email	T.Marshall/G.Scott - The FDA participants - May 23, 2007 teleconference regarding NDA 22-081	2007-06-05_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf	22-081
1	Regulatory	US	6/5/2007	Book 5	FDA Correspondence - Phone	L.Tanner/D.Brum. Two phone calls on 06/04/07 and 06/05/0. Process for finalizing Medication Guide, PI, and RiskMAP	2007-06-05_22081_CORR_PHONE_LTANNER_DBRUM.pdf	22-081

1	Regulatory	US	**6/4/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. RiskMAP revised proposal.	**2007-06-04_22081_CORR_EMAIL_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**6/2/2007**	Book 5	FDA Correspondence - Email	D.Brum/L.Tanner - MedGuide and PI	**2007-06-02_22081_CORR_EMAIL_DBRUM_LTANNER.pdf**	22-081
1	Regulatory	US	**6/1/2007**	Book 5	FDA Correspondence - Email	T.Marshall/S.Goldie. The response to CMC specification changes discussed during May 23, 2007 CMC teleconference. NDA 22-081 Amendment 0017 attached.	**2007-06-01_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf**	22-081
1	Regulatory	US	**6/1/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. E-mail from Dan Brum, FDA Project Manager, who has requested that Gilead resend the Medication Guide for ambrisentan that "looks" like Tracleer. Attached are the Medication Guides for Tracleer and Letairis.	**2007-06-01_22081_CORR_EMAIL_DBRUM_LTANNER_1.pdf**	22-081
1	Regulatory	US	**6/1/2007**	Book 5	FDA Correspondence - Phone	L.Tanner/D.Brum. Subject: Process for resolving PI Issues. FDA Minutes from 25 May 2007 Teleconference. Company Audit Details Dr.Galie.	**2007-06-01_22081_CORR_PHONE_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**6/1/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Email with two attachments. Subject: The Gilead details of the audit at Dr. Galie's site.	**2007-06-01_22081_CORR_EMAIL_DBRUM_LTANNER.pdf**	22-081
1	Regulatory	US	**6/1/2007**	Book 5	FDA Correspondence - Email - Meeting Minutes from May 25, 2007	D.Brum/L.Tanner. Email with the FDA Meeting Minutes from May 25, 2007.	**2007-06-01_22081_CORR_EMAIL_DBRUM_LTANNER_2.pdf**	22-081
1	Regulatory	US	**5/31/2007**	Book 5	FDA Correspondence - Phone	L.Tanner/D.Brum - Phone contacts, May 18 - May 31, 2007. Subjects: Response to preliminary RiskMAP comments and finalization of RiskMAP. FDA comments to PI.	**2007-05-31_22081_CORR_PHONE_LTANNER_DBRUM.pdf**	22-081
1	Regulatory	US	**5/31/2007**	Book 5	FDA (DDMAC) Correspondence - Fax	J.Acbay/L.M.Hubbard. Fax regarding NDA 22-081 Letairis MACMIS ID # 15246. Comments from the DDMAC on the first submission.	**2007-05-31_22081_CORR_DDMAC_FAX.pdf**	22-081
1	Regulatory	US	**5/30/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brunn. Response to FDA Comments to RiskMAP. Cover Letter (Amendment No. 16 to NDA 22-081) attached.	**2007-05-30_22081_CORR_EMAIL_LTANNER_DBRUM.pdf**	22-081

1	Regulatory	US	**5/25/2007**	Book 5	FDA Correspondence - Email	L.Tanner/M.Gordon. 7 day report; CRF 248-001-2020	**2007-05-25_22081_CORR_EMAIL_LTANNER_MGORDON.pdf**	22-081
1	Regulatory	US	**5/24/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Confirm Teleconference Time (2:30 EDT) and addition of Jennifer Stewart as a Participant.	**2007-05-24_22081_CORR_EMAIL_DBRUM_LTANNER_3.pdf**	22-081
1	Regulatory	US	**5/24/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Acceptability of Revised Labeling (Primary and Secondary Packaging). NDA 22-081.	**2007-05-24_22081_CORR_EMAIL_DBRUM_LTANNER_2.pdf**	22-081
1	Regulatory	US	**5/24/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. RiskMAP Questions	**2007-05-24_22081_CORR_EMAIL_DBRUM_LTANNER_1.pdf**	22-081
1	Regulatory	US	**5/24/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. FDA comments to Packaging	**2007-05-24_22081_CORR_EMAIL_DBRUM_LTANNER.pdf**	22-081
1	Regulatory	US	**5/23/2007**	Book 5	FDA Correspondence - Email	T.Marshall/S.Goldie. Ambrisentan Registration Tablets Dissolutions Data.	**2007-05-23_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf**	22-081
1	Regulatory	US	**5/22/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Confirmation of Participants and Call-in Number for FDA-Gilead Teleconference 05/25/2007.	**2007-05-22_22081_CORR_EMAIL_DBRUM_LTANNER_1.pdf**	22-081
1	Regulatory	US	**5/21/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Clarification for Processes in Reviewing the RiskMAP; Including attachment of Meeting Minutes from March 29, 2007 teleconference with FDA.	**2007-05-21_22081_CORR_EMAIL_DBRUM_LTANNER_1.pdf**	22-081
1	Regulatory	US	**5/21/2007**	Book 5	FDA Correspondence - Email	L.Tanner/D.Brum. Acceptability of Revised Labeling (Primary and Secondary Packaging). NDA 22-081.	**2007-05-21_22081_CORR_EMAIL_DBRUM_LTANNER.pdf**	22-081
1	Regulatory	US	**5/17/2007**	Book 5	FDA Correspondence - Letter	E.Fromm/L.Tanner. Discipline Review Letter. The comments on the RiskMAP portion of NDA 22-081 from the Office of Surveillance and Epidemiology.	**2007-05-17_22081_CORR_LETTER_EFROMM_LTANNER.pdf**	22-081
1	Regulatory	US	**5/14/2007**	Book 5	FDA Correspondence - Phone	T.Marshall/S.Goldie (Calles made on 4/30/07, 05/02/07, 05/03/07, 05/08/07, 05/14/07) - CMC Information Request, NDA Amendment 13: Updating List of Establishments and Pre-Approval Inspections. NDA 22-081.	**2007-05-14_22081_CORR_PHONE_SGOLDIE_TMARSHALL.pdf**	22-081

1	Regulatory	US	5/11/2007	Book 5	FDA Correspondence - Letter	L.Tanner/D.Brum. Desk Copies. 022081 - Amendment No. 14. Briefing Document for 25 May 2007	2007-05-14_22081_CORR_EMAIL_DBRUM_LTANNER.pdf	22-081
1	Regulatory	US	5/9/2007	Book 5	FDA Correspondence - Email	T.Marshall/S.Goldie - Response to the 8 comments/questions letter from 04/30/2007 . NDA 22-081	2007-05-09_22081_CORR_EMAIL_SGOLDIE_TMARSHALL.pdf	22-081
1	Regulatory	US	5/7/2007	Book 5	FDA Correspondence - Phone	L.Tanner/M.Robb. Three calls on 5/03/07, 5/04/07 and 05/07/07 - Subject: Processing during labeling	2007-05-07_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	5/7/2007	Book 5	FDA Correspondence - Email	L.Tanner/M.Robb - Subject: FedEx Shipment Notification from M.Robb (FDA).	2007-05-07_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	5/4/2007	Temp 7	FDA (DDMAC) Submission - NDA 22-081	**DDMAC Promotional Materials for NDA 22-081. Request for Perspective Review and Advisory Comments for Product Launch Materials for NDA 22-081 Latairis™ (ambrisentan 5 mg and 10 mg tablets) GSI Ref. No.000.**	2007-05-04_22081_CORR_DDMAC_PROMO_MATERIALS.pdf	22-081
1	Regulatory	US	5/3/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Subject: Response to DMETS, including revised labeling.	2007-05-03_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	5/1/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Gordon - Subject: Response to Clinical Questions. NDA 22-081	2007-05-01_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	5/1/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Subject: Updated PI Incorporating DMETS Recommendations (Version 1).	2007-05-01_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Letter	R.Sood/T.Marshall. Information request letter from FDA (review and comments of CMC section for NDA 22-081).	2007-04-30_22081_CORR_LETTER_RSOOD_TMARSHALL.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb. Two phone calls on 4/27/07 and 4/30/07. Subject: Briefing document for May 25 teleconference to discuss proposal to measure 6MWD at trough and peak. NDA 22-081.	2007-04-30_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/30/2007	Book 4	FDA Correspondence - Fax	S.Goldie/T.Marshall. Information Request Letter included. NDA 22-081.	2007-04-30_22081_CORR_FAX_SGOLDIE_TMARSHALL.pdf	22-081

1	Regulatory	US	**4/26/2007**	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb - Three phone calls on 4/20/07, 4/24/07, 4/26/07. Subject: Plan Promotional Materials; DMETS Comments; Process Labeling Revisions NDA 22-081	**2007-04-26_22081_CORR_PHONE_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**4/26/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Subject: Proposed plan for submitting promotional materials for use with the first 120 days post-approval.. NDA 22-081	**2007-04-26_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**4/24/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Regarding proposed plan for submitting promotional materials for use with the first 120 days post-approval.. NDA 22-081	**2007-04-24_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**4/23/2007**	Book 4	FDA Correspondence - Letter	E.Fromm/L.Tanner -Discipline Review Letter from FDA, Office of Surveillance and Epidemiology's DMETS. NDA 22-081	**2007-04-23_22081_CORR_Letter_LTANNER_EFROMM.pdf**	22-081
1	Regulatory	US	**4/23/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Response regarding randomization. NDA 22-081	**2007-04-23_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**4/19/2007**	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to Questions Regarding Bioanalytical Assay Issues; NDA 22-081	**2007-04-19_22081_CORR_EMAIL_LTANNER_PHINDERLING_2.pdf**	22-081
1	Regulatory	US	**4/19/2007**	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to additional request Multimedia Dissolution Profiles; NDA 22-081	**2007-04-19_22081_CORR_EMAIL_LTANNER_PHINDERLING_1.pdf**	22-081
1	Regulatory	US	**4/19/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - NDA 22-08; Follow-up information to Clinical Review Question 4 from e-mail dated 09 March 2007.	**2007-04-19_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**4/17/2007**	Book 4	FDA Correspondence - Phone	T.Marshall/S.Goldie - Three phone calls on 04/09/07, 04/16/07 and 04/17/07 Subject: Proposed "CMC" Amendment to Ambrisentan NDA to revise listed establishments/functions and to provide corrections to typos/minor errors. NDA 22-081	**2007-04-17_22081_CORR_PHONE_TMARSHALL_SGOLDIE.pdf**	22-081
1	Regulatory	US	**4/17/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Meeting to discuss Dosing Interval; Follow-up to March 29 Meeting. NDA 22-081	**2007-04-17_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081

1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Fax	M.Robb/L.Tanner - The FDA Teleconference Meeting Minutes (March 29, 2007). NDA 22-081.	2007-04-16_22081_CORR_FAX_LTANNER_MROBB_MEETING_MINUTES.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Follow-up email to request validation dilution.	2007-04-16_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm the date and time for teleconference (Amendment to AMB-323). Confirm name of new Project Manager. NDA 22-081	2007-04-16_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/16/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to Questions Regarding Dissolution Profiles; NDA 22-081	2007-04-16_22081_CORR_EMAIL_LTANNER_PHINDERLING_1.pdf	22-081
1	Regulatory	US	4/13/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Teleconference: Advice Clinical Inspection.	2007-04-13_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/13/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb - Phone calls on 04/12/07 and 04/13/07 - Clinical Inspection for Site #207 (Nazzareno	2007-04-13_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/12/2007	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Email to M. Robb indicating that Gilead acknowledged and understood the Clinical Pharmacology issues that P. Hinderling addressed in his written comments (03/29/07 - FDA teleconference). NDA 22-081	2007-04-12_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/12/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Response to Questions Regarding Dissolution Profiles; NDA 22-081	2007-04-12_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	4/9/2007	Book 4	FDA Correspondence - Phone	L.Tanner/M.Robb. Subject: Status of scheduling teleconference regarding plan to support once-daily dosing. Submission of promotional materials.	2007-04-09_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	4/5/2007	Book 4	FDA Correspondence - Email	L.Tanner/P.Hinderling - Request from P. Hinderling requesting F2 tests of respective dissolution profiles are various pHs for clinical and commercial products.	2007-04-05_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081

1	Regulatory	US	**4/4/2007**	Book 4	FDA Correspondence - Phone	L.Curran/V.Ventura - Clarification of submission format. NDA 22-081	**2007-04-04_22081_CORR_PHONE_LCURRAN_VVENTURA.pdf**	22-081
1	Regulatory	US	**4/3/2007**	Book 4	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Meeting to discuss Dosing Interval; Follow-up to March 29 Meeting. NDA 22-081	**2007-04-03_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/28/2007**	Book 3	FDA Correspondence - Phone	L.Tanner/M.Robb. Three phone calls on 03/26/07, 03/27/07and 03/28/07. Subjects: Preparation for March 29, 2007 90-Day Teleconference (NDA review status). Amendment No.8. Issues with e-mails sent to Melissa Robb. NDA 22-081.	**2007-03-28_22081_CORR_PHONE_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/28/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Summary of Amendments submitted or will be submitted to NDA 22-081.	**2007-03-28_22081_CORR_EMAIL_LTANNER_MROBB_1.pdf**	22-081
1	Regulatory	US	**3/28/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Plan for submitting electronic datasets are acceptable.	**2007-03-28_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/27/2007**	Book 3	FDA Correspondence - Fax	L.Tanner/M.Robb - Pre-Meeting Comments NDA 22-081	**2007-03-27_22081_CORR_FAX_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/27/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Revised List of Gilead Participants and Call-in Number. NDA 22-081	**2007-03-27_22081_CORR_EMAIL_LTANNER_MROBB_2.pdf**	22-081
1	Regulatory	US	**3/27/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - List of Gilead Participants and Call-in Number. NDA 22-081	**2007-03-27_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/26/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Response to questions in e-mail dated 9/03/07; Amendment No. 8; NDA 22-081	**2007-03-26_22081_CORR_EMAIL_LTANNER_MROBB_1.pdf**	22-081
1	Regulatory	US	**3/26/2007**	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Word questions submitted in meeting request (Amendment No.5). NDA 22-081	**2007-03-26_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**3/22/2007**	Book 3	FDA Correspondence - Phone	M.Plamondon/E.Smith - Mr. Smith was following up on Gilead Colorado's registration as a manufacturer.	**2007-03-22_22081_CORR_PHONE_MPLAMONDON_ESMITH.pdf**	22-081

1	Regulatory	US	3/20/2007	Book 3	FDA Correspondence - Phone	L.Tanner/S.Gershon - FDA Inspection for Site # 207 (Nazzareno Galie) Italy. NDA 22-081	2007-03-20_22081_CORR_PHONE_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	3/20/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Gilead Response to FDA regarding the request for Efficacy and Safety Datasets AMB-220, AMB-222, PK/PD PopPK. NDA 22-081	2007-03-20_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/19/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Request for Efficacy and Safety Datasets AMB-220, AMB-222, PK/PD PopPK. NDA 22-081	2007-03-19_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/13/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - The PDF file of Amendment No. 6. NDA 22-081.	2007-03-13_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/13/2007	Book 3	FDA Correspondence - Phone	L.Tanner/M.Robb (Phone calls on 03/05/07, 03/06/07, 03/08/07& 03/13/07) - Status feedback Letairis; Meeting request. NDA 22-081	2007-03-13_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Phone	L.Tanner/S.Gershon - The official contact report with Sharon Gershon regarding the status of the inspection of Dr. Galie (Italy)	2007-03-09_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Email	L.Tanner/P.Hinderling - Formatting Changes and Instructions for PI. NDA 22-081	2007-03-09_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	3/9/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Ambrisentan Questions. NDA 22-081.	2007-03-09_22081_CORR_EMAIL_MROBB_LTANNER.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb -The e-mail sent to Melissa Robb inquiring about the status of the proprietary name of LETAIRIS. (Note: This question was answered in a teleconference report dated 3-13-07 to Melissa Robb). NDA 22-081	2007-03-08_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Email	L.Tanner/P.Hinderling - Formatting Changes and Instructions for PI. NDA 22-081	2007-03-08_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	3/8/2007	Book 3	FDA Correspondence - Fax	M.Robb/L.Tanner - Teleconference meeting conformation - March 29, 2007. NDA 22-081.	2007-03-08_22081_CORR_FAX_MROBB_LTANNER.pdf	22-081

1	Regulatory	US	3/7/2007	Book 3	FDA Correspondence - Email	L.Tanner/P.Hinderling - Unformatted PI for Ambrisentan; NDA 22-081; Option to resolve formatting PI.	2007-03-07_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	3/6/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Gordon - Formal Response on Clinically Significant Abnormal ECGs. NDA 22-081.	2007-03-06_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	3/6/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - Unformatted PI for Ambrisentan - No need to submit to the NDA. 22-081.	2007-03-06_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/5/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb/P.Hinderling - Unformatted PI for Ambrisentan; NDA 22-081.	2007-03-05_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/3/2007	Book 3	FDA Correspondence - Email	L.Tanner/M.Robb - request for the meeting to discuss status of review of NDA 22-081. Update on Amendments submitted to NDA. Amendment 5 attached.	2007-03-03_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	3/2/2007	Book 3	FDA Correspondence - Phone	L.Tanner/P.Hinderling - Request for unformatted PI for internal edits. NDA 22-081	2007-03-02_22081_CORR_PHONE_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	2/27/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon - The initial response regarding clinically significant abnormal ECGs which was submitted to Mary Gordon on 02/27/07. NDA 22-081	2007-02-27_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	2/22/2007	Book 2	FDA Correspondence - CD-ROM	Desk Copy Request for Phase I CRF's. NDA 22-081	Request_for_Phase_I_CRFS- Desk _Copy	22-081
1	Regulatory	US	2/21/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Robb - Response to Filing Communication; Process for Submitting Completed Nonclinical Study not previously submitted in the NDA; Process for requesting meeting to discuss status of NDA. 22-081.	2007-02-21_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	2/21/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon. The FDA e-mail contact report that provides the plan to provide Maryann Gordon the CRFs that were not previously submitted for subjects who discontinued from Phase 1 studies. NDA 22-081.	2007-02-21_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081

1	Regulatory	US	2/20/2007	Book 2	FDA Correspondence - Email	The E-mail with Maryann Gordon regarding our intention to provide the CRF for Subject 38 in Study EE-001. NDA 22-081	2007-02-20_22081_CORR_EMAIL_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Letter	N.Stockbridge/M.Gerber - Filling Communication. Filling accepted and priority filling granted. NDA 22-081.	2007-02-16_22081_CORR_LETTER_NSTOCKBRIDGE_MGERBER.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Robb - Phone on 02/13/07, 02/14/07, 02/16/07 to confirm status of NDA filing letter and process for formally submitting responses that have already been emailed to reviewers. NDA 22-081	2007-02-16_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - RE: NDA 22-081; Status of Feedback Regarding Acceptability of Trade name LETAIRIS (Amendment No. 1)	2007-02-16_22081_CORR_EMAIL_MROBB_LTANNER.pdf	22-081
1	Regulatory	US	2/16/2007	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - E-mail response to Melissa Robb regarding how refills would be handled in the RiskMAP.	2007-02-16_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	2/15/2007	Book 2	FDA Correspondence - Email	L.Tanner/P.Hinderling - Summary of PT and INR Methodology. Protime Summary Information doc. Attached.	2007-02-15_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Phone	Phone - Nikolas Burlew (Regulus Pharmaceutical) called Nancy Schmidt (FDA-Denver District) to establish registration for Gilead Colorado.	2007-02-14_22081_CORR_PHONE_NBURLEW_NSCHMIDT.pdf	22-081
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Email	M.Robb/L.Tanner/ - Email from M. Robb with additional question.(Ambrisentan and RiskMAP). NDA 22-81	2007-02-14_22081_CORR_EMAIL_LTANNER_MROBB.pdf	22-081
1	Regulatory	US	2/14/2007	Book 2	FDA Correspondence - Email	L.Tanner/P.Hinderling - Email indicating that Gilead is continuing to work with our vendor to obtain the PT and INR methodology for AMB-106. NDA 22-081	2007-02-14_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf	22-081
1	Regulatory	US	2/13/2007	Book 2	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm for handling requests directly from reviewer. E-mail dated 2/13/07 regarding RiskMAP and distribution. Filling Letter.	2007-02-13_22081_CORR_PHONE_LTANNER_MROBB.pdf	22-081

1	Regulatory	US	**2/13/2007**	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - Gilead response to the questions from FDA on the distribution of Ambrisentan and RiskMAP. The patient enrollment form attached. NDA 22-081	**2007-02-13_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**2/12/2007**	Book 2	FDA Correspondence - Phone	M.Gordon/H.Isokoski. Maryann Gordon called and request to talk to L. Tanner. NDA 22-081	**2007-02-12_22081_CORR_PHONE_MGORDON_HISOKOSKI.pdf**	22-081
1	Regulatory	US	**2/12/2007**	Book 2	FDA Correspondence - Email	M.Gordon/L.Tanner - Another E-mail from Maryann Gordon asking that we submit all clinical information sent to her formally to the NDA.	**2007-02-12_22081_CORR_EMAIL_MGORDON_LTANNER.pdf**	22-081
1	Regulatory	US	**2/12/2007**	Book 2	FDA Correspondence - Email	M.Gordon/L.Tanner - E-mail contact report with Maryann Gordon regarding regenerating a table for LFTs from AMB-222 for archival in the database.	**2007-02-12_22081_CORR_EMAIL_LTANNER_MGORDON.pdf**	22-081
1	Regulatory	US	**2/12/2007**	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - FDA questions on the distribution of Ambrisentan and RiskMAP.	**2007-02-12_22081_CORR_EMAIL_LTANNER_MROBB.pdf**	22-081
1	Regulatory	US	**2/9/2007**	Book 2	FDA Correspondence - Phone	L.Tanner/M.Gordon - Confirm the requirements for clinical information requested in emails dated 02/07/07 & 02/09/07.	**2007-02-09_22081_CORR_PHONE_LTANNER_MGORDON.pdf**	22-081
1	Regulatory	US	**2/9/2007**	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon - email sent to M.Gordon regarding her request for additional clinical information. The e-mail contains all of the attachments. NDA 22-081.	**2007-02-09_22081_CORR_EMAIL_LTANNER_MGORDON.pdf**	22-081
1	Regulatory	US	**2/9/2007**	Book 2	FDA Correspondence - Email	E-mail from Peter Hinderling conforming that he received the replacement pages for EE-002	**2007-02-09_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf**	22-081
1	Regulatory	US	**2/8/2007**	Book 2	FDA Correspondence - Email	E-mail that was submitted to Peter Hinderling, Clinical Pharmacology Reviewer, which contains the replacement pages with figures that are easier to read from EE-002 at his request.	**2007-02-08_22081_CORR_EMAIL_LTANNER_PHINDERLING.pdf**	22-081
1	Regulatory	US	**2/8/2007**	Book 2	FDA Correspondence - Email	L.Tanner/M.Gordon - Conformation of Teleconference on Friday, February 9, 10:00 a.m. EST	**2007-02-08_22081_CORR_EMAIL_LTANNER_MGORDON.pdf**	22-081

1	Regulatory	US	**2/8/2007**	Book 2	FDA Correspondence - Phone	M.Gordon/L.Tanner - Schedule time for teleconference to discuss process for capturing lab values.	**2007-02-08_22081_CORR_PHONE_MGORDON_LTANNER.pdf**	22-081
1	Regulatory	US	**2/6/2007**	Book 2	FDA Correspondence - Phone	H.Isokoski/P.Hinderling - The Methodology to determine Prothrombin Time (PT) and International Normalized Ratio (INR) in AMB-106 and Legible Figures for the report EE-002.	**2007-02-06_22081_CORR_PHONE_PHINDERLING_HISOKOSKI.pdf**	22-081
1	Regulatory	US	**2/5/2007**	Book 2	FDA Correspondence - Email	L.Tanner/M.Robb - E-mail correspondence; Request for Location QTc documentation; Clinical Pharmacology Summary Table. The FDA Response, 2006 Clin. Final IB and FDA Notification App. Attached.	**2007-02-05_22081_CORR_EMAIL_LTANNER_MROBB_.pdf**	22-081
1	Regulatory	US	**2/2/2007**	Book 1	FDA Correspondence - Email	L.Tanner/S.Gershon - Confirm that CD's were sent with information for Clinical Inspections. Attached to the email is the cover letter.	**2007-02-02_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf**	22-081
1	Regulatory	US	**2/2/2007**	Book 1	FDA Correspondence - Phone	L.Tanner/M.Gordon - Confirm that Maryann Gordon was able to retrieve the CRF for Subject 109-002.	**2007-02-02_22081_CORR_PHONE_MGORDON_LTANNER.pdf**	22-081
1	Regulatory	US	**2/2/2007**	Book 1	FDA Correspondence - CD-ROM	Desk Copy Request for Site Specific Information. NDA 22-081	**Clinical_Inspection_Request-Desk_Copy**	22-081
1	Regulatory	US	**2/1/2007**	Book 1	FDA Correspondence - Phone	E.Smith/L.Tanner & M.Plamondon - E.Smith of the Denver District Office of the FDA called regarding the ambrisentan NDA.	**2007-02-01_22081_CORR_PHONE_ESMITH_LTANNER_MPLAMONDON_.pdf**	22-081
1	Regulatory	US	**2/1/2007**	Book 1	FDA Correspondence - Phone	L.Tanner/M.Gordon - Clarify whether CRF for Subject 109-002 was submitted in NDA	**2007-02-01_22081_CORR_PHONE_LTANNER_MGORDON.pdf**	22-081
1	Regulatory	US	**2/1/2007**	Book 1	FDA Correspondence - Email	S.Gershon/L.Tanner - Conform Information to be provided on CD's; Clinical Inspections NDA 22-081.	**2007-02-01_22081_CORR_EMAIL_SGERSHON_LTANNER.pdf**	22-081
1	Regulatory	US	**1/31/2007**	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Conformation that CRF's for subject 156-007 and 126-008 was received at FDA.	**2007-01-31_22081_CORR_EMAIL_LTANNER_MROBB_156-007.pdf**	22-081

1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L.Tanner/S.Gershon - Confirm acceptability of listings that will be included in the information package on the CDs that will be submitted to her for use during the FDA clinical inspections.	2007-01-30_22081_CORR_PHONE_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Robb - Confirm that Amendment #2 was received at FDA on January 30, 2007. NDA 22-081.	2007-01-30_22081_CORR_PHONE_LTANNER_MROBB_156-007.pdf	22-081
1	Regulatory	US	1/30/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Gordon - Death of female subject (221-003) enrolled in the extension study (AMB-32/321-3). NDA 22-081	2007-01-30_22081_CORR_PHONE_LTANNER_MGORDON.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - CRF for Subject 156-007 requested by Dr. Marciniak; NDA 22-081. (156-007.zip attached)	2007-01-26_22081_CORR_EMAIL_LTANNER_MROBB_156-007.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - CRF for subject 126-008 requested by Dr. Marciniak; NDA 22-081. (126-008.zip attached)	2007-01-26_22081_CORR_EMAIL_LTANNER_MROBB_126-008.pdf	22-081
1	Regulatory	US	1/26/2007	Book 1	FDA Correspondence - Email	L.Tanner/S.Gershon - Confirm information to be provided on CD's; Clinical Inspections NDA 22-081	2007-01-26_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Phone	L.Tanner/S.Gershon - Reminder for non-USA contact information for Site #207 (Nazzareno Galie, Italy) NDA 22-08.	2007-01-25_22081_CORR_PHONE_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Email	L.Tanner/S.Gershon - Contact Information Italian Inspector; NDA 22-081 (ambrisentan)	2007-01-25_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/25/2007	Book 1	FDA Correspondence - Email	S.Gershon/ L.Tanner - Contact Person in Italy.	2007-01-25_22081_CORR_EMAIL_SGERSHON_LTANNER_.pdf	22-081
1	Regulatory	US	1/23/2007	Book 1	FDA Correspondence - Email	M.Robb/L.Tanner - Email - Response from FDA to the letter dated 1/11/07. Re: Submission of complete CRF's: NDA 022-081.	2007-01-23_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/22/2007	Book 1	FDA Correspondence - Email	S.GershonL/Tanner - Email regarding Revised Protocol Document - Presence of Sponsors Clinical Investigations.	2007-01-22_22081_CORR_EMAIL_SGERSHON_LTANNER_.pdf	22-081

1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence -Phone	S.GershonL/Tanner - Phone regarding FDA inspections at clinical sites that conducted Phase 3 studies AMB-320 or AMB-321.	2007-01-19_22081_CORR_PHONE_SGERSHON_LTANNER_.pdf	22-081
1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Email	L.Tanner/S.Gershon. Email regarding revised protocol documents. AMB-321 & AMB 320 protocols attached.	2007-01-19_22081_CORR_EMAIL_LTANNER_SGERSHON.pdf	22-081
1	Regulatory	US	1/19/2007	Book 1	FDA Correspondence - Email	S.Gershon/ L.Tanner - Email regarding NDA 22-081 Letairis . Respond from CDER about DSI inspections.	2007-01-19_22081_CORR_EMAIL_SGERSHON_LTANNER_.pdf	22-081
1	Regulatory	US	1/18/2007	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Response to FDA Letter Dated 1/11/07 Re: Submission of Complete CRF's, NDA 022-081	2007-01-18_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/16/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Robb - Follow-up on response to Division regarding re-submission of CRF's and filing process.	2007-01-16_22081_CORR_PHONE_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/16/2007	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Clarification on the requested presented during the teleconference on 1/9/07. The Response to Division regarding re-submission of CRF's and filing	2007-01-16_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Letter	Letter from E.Fromm/M.Gerber. Discipline Review Letter - CRF's Forms in the NDA 20-081	2007-01-11_22081_CORR_LETTER_EFROOM_MGERBER.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Email	Email from M. Robb to H.Isokoski with the discipline review letter from FDA.	2007-01-11_22081_CORR_EMAIL_MROBB_HISOKOSKI_1.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Email	H.Isokoski/M.Robb - Email. Clarification on the requested, presented during the teleconference on 01/09/07.	2007-01-11_22081_CORR_EMAIL_MROBB_HISOKOSKI_.pdf	22-081
1	Regulatory	US	1/11/2007	Book 1	FDA Correspondence - Phone	H.Isokoski/M.Robb - Three phone calls. Clarification on the teleconference held on 01/09/07.	2007-01-11_22081_CORR_PHONE_HISOKOSKI_MROBB.pdf	22-081
1	Regulatory	US	1/10/2007	Book 1	FDA Correspondence - Letter	E.Fromm/L.Tanner - FDA letter that acknowledges that the date of receipt of NDA 22-081 was December 18, 2006. The official filing data will be February 16, 2007	2007-01-10_22081_CORR_LETTER_EFROOM_LTANNER.pdf	22-081

1	Regulatory	US	1/9/2007	Book 1	FDA Correspondence - Phone	Gilead Teleconference Meeting Minutes with FDA - T. Marciniak.	2007-01-09_22081_CORR_PHONE_MEETING_MINUTES_TMARCINIAK_HISOKOSKI.pdf	22-081
1	Regulatory	US	1/5/2007	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Email. Confirmation of teleconference scheduled for Tuesday, January 9, 2007 with the FDA.	2007-01-05_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	1/5/2007	Book 1	FDA Correspondence - Phone	L.Tanner/M.Robb - Phone to confirm date and time and participants for teleconference with the FDA.	2007-01-05_22081_CORR_PHONE_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	12/19/2006	Book 1	FDA Correspondence - Phone	L.Tanner/M.Robb - Feedback from M. Robb regarding the process for responding to the Division of DMETS regarding the acceptability of LETAIRIS. Attached FDA contact report from 12/18/2006 per L. Tanner.	2006-12-19_22081_CORR_PHONE_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	12/19/2006	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Confirmation from M.Robb that the submission NDA 22-081 was received at document room.	2006-12-19_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081
1	Regulatory	US	12/18/2006	Book 1	FDA Correspondence - Email	L.Tanner/M.Robb - Conformation that NDA 22-081 was received at FDA Mail Room.	2006-12-18_22081_CORR_EMAIL_MROBB_LTANNER_.pdf	22-081

EXHIBIT
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U.S. PATENT NO. 7,109,205

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT		
1. Enter the number of days for the testing phase as defined in 37 CFR 1.775(c)(1)		1629
2. Enter the number of days for the approval phase as defined in 37 CFR 1.775(c)(2)		180
3. Add line 1 and line 2 and enter the total here	1809	
4. Enter the number of days of the period of line 2 which occurred prior to the issue date of the patent		0
5. Enter the number of days the period of line 2 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)		0
6. Add line 4 and line 5 and enter the total here	0	
7. Subtract line 6 from line 3 and enter the difference here (if less than zero enter 0)	1809	
8. Enter the number of days of the period of line 1 which occurred prior to the issue date of the patent		1539
9. Enter the number of days of the period of line 1 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)		0
10. Add line 8 and line 9 and enter the total here	1539	
11. Subtract line 10 from line 7 and enter the difference here	270	
12. Enter the number of days from line 1		1629
13. Enter the number of days from line 10		1539
14. Subtract line 13 from line 12 and enter the difference here (if less than zero enter 0)		90
15. Multiply line 14 by 0.5 (one half) and enter the amount here	45	
16. Subtract line 15 from line 11 and enter the difference here (if less than zero enter 0)	225	
17. Enter the original expiration date of the patent		10.07.15
18. Enter the expiration date of the patent if extended by the number of days on line 16		05.19.16
19. Enter the date of the FDA (Food and Drug Administration) final approval		06.15.07
20. Limitation set forth in 37 CFR 1.775(d)(3)		14 years
21. Add the number of years on line 20 to the date on line 19 and enter the revised date here		06.15.21
22. Enter the earlier date appearing on line 18 or line 21	05.19.16	
23. Enter the original expiration date of the patent (from line 17)		10.07.15
24. Check one of the following three boxes and enter the listed time period here		5 years
[redacted] The patent issued after 24/9/84 — 5 Years	X	
The patent issued prior to 24/9/84 and no request for exemption as defined in 37 CFR 1.775(d)(6)(i) was filed prior to 24/9/84 — 5 Years		
The patent issued prior to 24/9/84 and an exemption as defined in 37 CFR 1.775(d)(6)(ii) was filed prior to 24/9/84 — 2 Years		
25. Add the number of years on line 24 to the date on line 23 and enter the revised date here		10.07.20
26. Enter the earlier date appearing on line 22 or line 25	05.19.16	
27. Enter the original expiration date of the patent (from line 17)	10.07.15	
28. Enter the number of days by which line 26 and line 27 differ here This is the length of patent term extension	225	

INFORMATION OBTAINED FROM THE U.S. PATENT AND TRADEMARK OFFICE